VOLUME 13 NUMBER 2

ENDOCRINOLOGY

THE BULLETIN OF THE ASSOCIATION
FOR THE STUDY OF

INTERNAL SECRETIONS

EDITORS

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MARCH-APRIL

1929

PUBLISHED BI-MONTHLY BY THE ASSOCIATION FOR THE STUDY OF INTERNAL SECRETIONS, SUITE 1214 WILSHIRE MEDICAL BLDG., LOS ANGELES, CALIFORNIA
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Vol. 13. No. 2. Serial No. 64 *March-April, 1929*

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Entered as second-class matter March 12, 1921, at the postoffice at Los Angeles, California, under the Act of March 3, 1879.

Acceptance for mailing at special rate of postage provided for in Section 1103, Act of October 3, 1917, authorized September 17, 1920.

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This Association is not limited to specialists. It includes in its membership physiologists and other investigators, in addition to a large number of physicians in active practice—leading men in this field in the United States and thirty other countries.

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Correspondence relating to advertising and business matters should be addressed to Endocrinology, 1214 Wilshire Medical Bldg., Los Angeles, California.

THE THIRTEENTH ANNUAL MEETING

The Thirteenth Annual Meeting of the Association for the Study of Internal Secretions will be held in the Municipal Auditorium, Portland, Oregon, Tuesday, July 9, 1929, with two sessions, 9 A. M. and 2 P. M.

The Auditorium is located in the block bounded by Second, Third, Market and Clay Streets, and will be the general headquarters of the A. M. A. Our meeting will be held in the room known as the "North Wing," second floor. There will be signs at the Auditorium directing to the room.

During the forenoon and afternoon sessions the following papers will be presented. Final program will be mailed to all members within a short time.

The Effects of Extracts of Testes in Correcting the Castrate Condition in the Fowl and in Mammals. Carl R. Moore, T. F. Gallagher and F. C. Koch, Chicago.

Endocrinologic Interpretation of Normal Development. Wm. Engelbach, St. Louis.

Endocrine Studies on Dementia Praecox. R. G. Hoskins, Boston, and F. H. Sleeper, Worcester.

A Further and Final Report on a Case of Tetanea Parathyreopriva, Treated for a Year with Collip's Parathyroid Extract, with Eventual Death and Autopsy. H. Clare Shepardson and H. Lisser, San Francisco.

Preliminary Note on the Assay of the Follicular Hormone by Vaginal Administration. H. H. Powers, J. R. Varley and J. A. Morrell, New Brunswick, N. J.

A Summary of a Study of 1100 Glucose Tolerance Tests. Henry J. John, Cleveland.

A Study of Blood Sugar Curves Before and After Thyroidectomy. Blair Holcomb, Portland.

Endocrine Regulation of Reproduction, Oscar Riddle, Cold Spring Harbor.

Some Aspects of the Mode of Action of the Betahormone of the Pituitary, Oliver Kamm, Detroit.

Nasal Spray Method of Administering Hormones of the Ovary and Pituitary Gland, J. P. Pratt and Merrill Smeltzer, Detroit.

Geographical Factors of Calcium Metabolism, Homer Wheelon, Seattle.

The Association of Diabetes Mellitus and Diabetes Insipidus, Frank N. Allen, Rochester, Minn.

Members have the privilege of inviting as guests any who may be interested in this subject. All subscribers to ENDOCRINOLOGY are invited to attend.

O. RIDDLE, President,
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THIRTEENTH ANNUAL BUSINESS MEETING

The Thirteenth Annual Business Meeting of the Association for the Study of Internal Secretions will convene at 5 o'clock the afternoon of Tuesday, July 9, 1929, in the Municipal Auditorium, Portland, Oregon.

The purpose of this meeting will be to receive reports for the fiscal year ended December 31, 1928, to elect officers for the ensuing year, and to transact any other business which may come before the Association.

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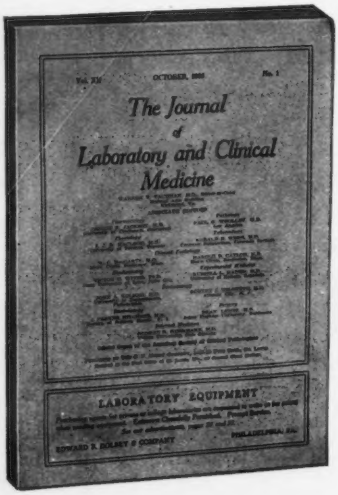
Published first of each month. Volumes begin with October of each year. Subscriptions may begin at any time. $8.50 per year under domestic postage, including the United States, Cuba, Mexico, Porto Rico, Canal Zone, Hawaii, and Philippines. Under Canadian and foreign postage, $8.90. Single copies, 75 cents.



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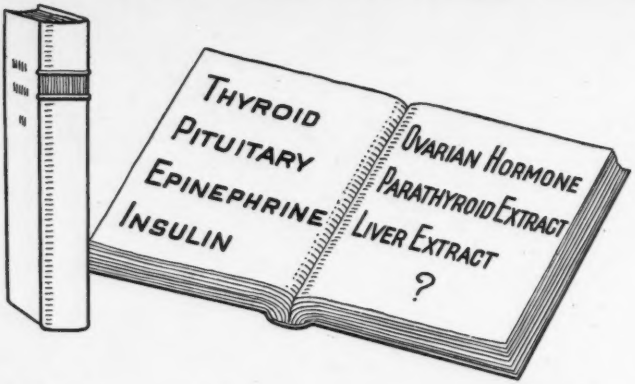

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Volume 13, Number 2 MARCH-APRIL, 1929 Serial No. 64

STUDIES OF THE ENDOCRINE GLANDS

VII. AN ANALYSIS OF FIVE HUNDRED CASES SIMULATING ENDOCRINE DISORDERS

CHARLES HENRY LAWRENCE, M.D.

AND

ALLAN WINTER ROWE, PH.D.

Evans Memorial

BOSTON, MASS.

PART I.

In a series of previous communications an objective method for the diagnosis of endocrine disorders has been outlined (1) and a group of clinical studies reported in which it has been applied (2).

In the large number of patients presenting outward evidence of possible endocrine disease (the present group is drawn from a series of over two thousand cases) it is not surprising that a due proportion of them on thorough examination should disclose a non-endocrine etiology. As our studies are concerned with the accurate differential diagnosis of the several endocrine morbidities, such cases form an intrinsic part of any general discussion. From our point of view they are primary in importance, as the basic principle of the diagnostic method is the proven elimination of all possible non-endocrine causes of an observed given result before it may be adduced to support an endocrine diagnosis. The present communication, therefore, deals with the findings from a number of non-endocrine conditions which either present stigmata offering seeming clinical evidence of the recognized endocrine disorders or duplicate the results of individual tests usually associated with some endocrine malfunction. An illustration of the first could be an obesity deriving from gluttony or an amenorrhea of cardiac or renal origin; of the second, the high basal rate associated with leukemia or the persistent glycosuria deriving from syphilis or a lesion of the central nervous system.

Further, speculative endocrinology has, from time to time, deduced from a single symptom a complicity of one or more ductless glands in a condition of known primary non-endocrine etiology. Objective analysis will confirm or deny the warrant of such inclusion and thus define criteria

for treatment which are beneficial in both a positive and a negative sense. The indiscriminate use of powerful glandular extracts has nothing to recommend it as a practice, while the results of an uncritical polypharmacy may be disastrous.

TABLE I

ETIOLOGICAL CLASSIFICATION

Group	Pathological Condition Detail	Primary	Cases Secondary	Total	Group Prim. Totals
	Normal Controls	18	—	18	18
Infections	Tuberculosis	19	7	26	
	Atrophic Rhinitis	4	—	4	
	Arthritis	18	6	24	56
	Gall Bladder Infections	10	3	13	
	Primary Focal Infections	5	20	25	
Psycho-Neurotic States	Neuroses	21	1	22	
	Psycho-Neuroses	24	9	33	60
	Psychoses	15	1	16	
Disorders of the Central Nervous System	Primary Lesions of the Central Nervous System	47	3	50	
	Epilepsy	9	1	10	
	Paralysis Agitans and Parkinson Syndrome	11	—	11	82
	Mental Arrest	3	5	8	
	Miscellaneous Nerve Diseases	12	1	13	
Disorders of Metabolism	Malnutrition	14	16	30	
	Obesity	12	5	17	35
	Gout	2	—	2	
	Miscellaneous Bone Diseases	7	3	10	
Disorders of the Cardio-Vascular System	Diseases of Heart	7	2	9	
	Diseases of Kidneys	22	31	53	61
	Cardio-Renal Disease	32	9	41	
Diseases of the Blood	Primary Anaemia	8	—	8	
	Secondary Anaemia	2	2	4	17
	Leukaemias (myel. and lym.)	6	—	6	
	Haemophilia	1	—	1	
Tumors	Tumors, Malignant	6	—	6	
	Tumors, Benign	6	4	10	20
	Goiter, Non-Toxic (1)	8	—	8	
Miscellaneous Diseases	Syphilis (acquired and congenital)	43	14	57	43
	Diseases of the Eye	5	9	14	5
	Diseases of the Ear	57	8	65	57
	Diseases of the Skin	17	6	23	17
	Diseases of Gastro-Intestinal Tract	10	5	15	10
	Diseases of Pelvis	6	4	10	6
	Asthma	11	1	12	11
	Intoxications	2	4	6	2
	Total	500	180	680	500

(1) Thyroid enlargements of endemic type with no evidence of any functional aberration.

For these several reasons, the cases presented in the series cover a wide range of disease conditions. Information concerning the general metabolism of some of these is a by-product of the primary investigation and will be discussed at another time. Not infrequently, in addition to the primary morbidity, a secondary condition would be apprehensible, of sufficient importance to warrant its inclusion in the general disease picture. These could be concomitant or resultant, but in either case they produce

symptoms which constitute an integral part of the general condition as presenting for diagnosis. To simplify later discussion, the etiological classification of the five hundred cases may be presented in tabular form.

The group classifications are intended only for convenience and are in some measure arbitrary. Other groupings would be equally open to criticism and would fail to embody the features upon which emphasis is to be placed. The figures presented have but minor statistical value as indicating relative incidence. The group of ear cases, for example, constitute a portion of a study on otosclerosis which has been reported in part elsewhere (3). Other individual conditions represent beginnings of studies which are now under way, as the Parkinsonians, the primary anaemias, and the leukaemias. Where selection has thus been exercised the number of cases recorded is of no significance. All of them, however, fall in on of the several categories outlined above.

Following the practice of the earlier papers in this series, a few of the physical measurements and significant statistics are collated in tabular form. To conserve space, the weight, chest and lung volume comparisons, using Dreyer's and West's standards under limitations already described, are also included.

TABLE II

PHYSICAL MEASUREMENTS AND "VITAL CAPACITY" COMPARISONS

No.	Sex		Obs.	Age	Height	Sitting Height	Chest	Weight	Lung Volume
	M.	F.							
500	37%	63%	High	78	193	100.5	125	145.0	5600
			Low	4	113	69	53.5	19.2	300
			Average	**36** yrs.	**164** cm.	**87** cm.	**79** cm.	**60.2** cm.	**2950** cc.
Sitting Height Index 0.530			"Vital Capacity"	High (%)			+56	+109	+23
				Low (%)			−23	−40	−89
				+Average (%)			**+9**	**+18**	**+5**
				%			52	44	15
Area 1.66 sq. m.				−Average (%)			**−7**	**−12**	**−24**
				%			48	56	85
				Net Average			**+2**	**+1**	**−20**

The female dominance in the sex proportion has already been commented on in the earlier papers where, in the endocrine conditions discussed, it is even more striking. That individual conditions fail to show this disparity (Syphilis: males, 28; females, 29) is lost in the method of presentation. Diseases of the female pelvis obviously play no part in our figures (see Table I). We are inclined to the belief that a more frequent resort to medical aid on the part of the female is a definite although unevaluable factor.

The ages show a wide range, although in fairness it must be said that young children play but a small part in the series. This is determined in no small measure by the inability of the young to give that measure of co-operation which is essential for the performance of the tests. Further,

the standards for childhood lack the clarity of outline determined for the adolescent and the adult. We have experienced the greatest difficulty in obtaining opportunity to study healthy children in order that such criteria might be established. For this reason we have been obliged, with much regret, to limit our studies, in largest measure, to those groups in which normal performance and the deviations induced by disease have both been defined by actual test and observation.

Extrapolation is always hazardous and peculiarly so when one must bridge so active a period of physiological readjustment as the early years of puberty. In the present series, only eleven children are less than eleven years of age, and of these but two are less than eight. These were two boys, respectively four and six, but both presenting unusual mental maturity coupled with an even more unusual capacity for obedience. In both cases the tests were entirely successful. The popular encouragement to self-expression in early childhood has deprived us vociferously of a number of potential studies.

The several physical measurements show an equally wide range. The maximum weight record of 145 kgm. was that of a so-called normal giant, a man of huge frame and complete normality of physical function. The averages throughout are definitely normal when due allowance is made for the relative sex influence in determining certain ratios. For example, the chest measurement predicted from the sitting height would be 82.8 cm. for the male and 75.5 cm. for the female (Dreyer). Weighting for relative sex influence, the predicted value becomes 78.2 cm., while the observed rounded average is 79 cm. This serves to illustrate both the absorption of large individual variations in any average computation and equally, the significance attaching to the variations (when presented by a single group), even though they be of small magnitude. This latter point has been stressed in the earlier endocrine papers. In them also has been emphasized the greater significance of relative values when comparisons are with standards making allowance for certain of the fixed variables. The so-called "Vital Capacity" comparisons embody this principle and the data gather an added import. The cases in the series show a rough equality in over- and under-weight. The former is the smaller group but is free from the natural limitation implicit in those below prediction; as a result, it balances in amount what is lacking in number and the net average deviates but 1 per cent away from prediction. The chest measurements, as is to be expected, parallel those for weight. With the lung volume, however, there is a sharp and significant departure from the normal. Only 15 per cent exceed prediction and then only to an inconsiderable amount. The net average shows a drop of 20 per cent from predicted to observed values. As has been previously stated, we have found Dreyer's male "A" and female "B" standards most nearly to conform to normal American relationships. In a recent monograph Myers (4) has presented a most valuable summary of the influence of cardiac and pulmonary disease on this quan-

tity. He concludes that lung volumes falling 15 per cent or more below the predicted level require careful examination. In addition to a variety of significant pathological states influencing lung volume unfavorably, he records others, chiefly residua, which are devoid of clinical import. Malingering and lack of co-operation are cited as factors to be reckoned with.

In our own experience the second of these assumes a very marked significance and one of us has emphasized its influence as clearly indicated where a long series of observations are made on the same patient (5). The asthenia of severe illness, irrespective of character, is a powerfully inhibiting influence (eight cases of primary anaemia averaged —41 per cent, and six of leukaemia—38 per cent), and low values are to be interpreted as due in part to weakness. In the present compilation, the importance resides in the low average produced by such a variety of conditions of which cardiac and respiratory conditions are only a small part.

As the cases of this group were studied primarily for their simulation of endocrine conditions or the possible presence of an endocrine element in the etiology, a brief comparison may be made with the results of the several endocrine series.

TABLE IIa

"VITAL CAPACITY" COMPARISONS

	Gland				
	Function	Pituitary	Thyroid	Ovary	Adrenals
Weight	−	+22	+10	+ 5	−11
	±	+12	+ 6	−	−
	+	+ 7	− 3	−	−
	Weighted Average...	+14	+ 7	+ 5	−11
Lung Volume	−	−19	−22	−19	−18
	±	−19	−22		
	+	−16	−39		
	Weighted Average...	−18	−24	−19	−18

The obesity of the pituitary and the emaciation of the adrenal cases show marked divergence from the non-endocrine average. The tendency of the hypofunctional endocrine states (exclusive of the adrenal) is here evidenced.

With the lung volume measurements, on the other hand, only the thyroid exceeds the loss shown by the non-endocrine group. It is striking that the subjects of adrenal deficiency in whom asthenia is a uniform and highly significant observation, show slightly smaller loss than does the group under discussion. The lack of representative character determined by the meager number of adrenal cases may conceivably be balanced against the appreciable number of approximately normal individuals which tend to raise the average in the non-endocrine group.

The results of analyses and tests using the urine as the medium of response, are collected in Table III.

TABLE III

URINE MEASUREMENTS

Urine Analysis		Phenol Sulphone Phthalein		Nitrogen Partition	
Observation	Amt.	Observation	Amt.	Observation	Amt.
Volume.....High (cc.)...	4600	1st Hour....Av. (%)....	35	Total N_2....Av. (gms.)...	**9.00**
Low (cc.)...	300	2nd Hour...Av. (%)....	20	Urea N_2....Av. (%)....	**81.1**
Average(cc.)	**1210**	Total.....Av. (%)....	**55**	Uric Acid...Av. (%)....	**2.3**
		High.....	90	Ammonia...Av. (%)....	**3.8**
Spec. Grav...High.....	1.037	Low.....	8	Creatinin...Av. (%)....	**4.5**
Low.....	1.005			Residual....Av. (%)....	**8.3**
Average....	**1.018**			%=or>9% (%)....	48
		Urea Curve			
Albumin (%).....	26	Normal (%).....	**54**		
Casts (%).....	19	Delayed (%).....	**11**	Misc. Tests	
Sugar (%).....	9	Progressive (%).....	**9**	Amylase Index, Av.....	14
"Urobilinogen" (No.)....	4[1]	Low (%).....	**26**	Salol, Av. (min.).....	71

[1] Four Cases of Primary Anaemia.

While certain of the cases showed a marked polyuria, the average elimination conforms to normal figures, as does that for the specific gravity. The appreciable percentage of cases showing albuminuria and casts includes not only the established kidney cases but numerous others in which nutritive disturbances, faulty posture, and similar factors are operative. The cases exhibiting glycosuria are interesting and significant. It is understood, of course, that no cases of pancreatic diabetes are included. They were excluded from the endocrine studies for reasons that have already been discussed and naturally may form no part of a group of non-endocrine diseases. The allocation of the glycosurias to the major etiological headings is informative.

TABLE III-a

Condition	No. of Cases
Lesions Central Nervous System	13
Psychoses	4
Syphilis	8
Gall Bladder Disease	4
Normal Pregnancy	1*
Asthma (Adrenalin)	1
Primary Anaemia	2
Leukaemia	2
Malignant Neoplasm	2
Total	37

The remaining eight cases were scattering and no direct cause of the glycosuria was ascertained. Malnutrition was not impossibly the cause in the majority of them. Alcoholism may have been a factor in two cases. While certain of these conditions are generally recognized as causative of low-grade glycosuria (lesions of the brain, gall bladder, pregnancy, etc.), comment may be permitted on certain others. In our experience, a slight

*Glucose and not Lactose.

glycosuria is the frequent accompaniment of syphilitic infection even when no evidence can be obtained of active involvement of the nervous system. It is also noteworthy that one-third of the leukaemic cases, one-fourth of the primary anaemias, and one-third of the cancer cases presented the same condition.*

As the endocrine cases (exclusive of the thyroid) show an incidence of nearly 25 per cent, the significance of the present observation is patent.

Reverting to Table III, another interesting observation lies in the occurrence of a positive "urobilinogen" test in four cases of primary anaemia. This test was first offered as an indication of liver disease but was shown by us to occur frequently in pituitary disorders. That positive response is not conditioned solely by the presence of urobilinogen in the urine, is highly probable. Like many color tests, the reaction is probably not specific.

The Phthalein test offers nothing distinctive, the low normal value agreeing with the findings in the endocrine series. The provocative urea curves equate well with the urine findings, one-fourth of them showing poor elimination. Low values do not always imply a lessened kidney permeability, as a number of cases of partial protein inanition exhibit the same phenomenon. Whether an analogy to the condition postulated in Folin's theory (6) of tissue absorption of ingested carbohydrate is operative here, remains to be determined. The relatively normal salol value is a modest bit of evidence for relative kidney integrity as it measures this function primarily, the indication of the level of gastric motility depending on normal elimination.

The Nitrogen Partition and its implications have been discussed in detail in the earlier papers. In brief, a residual nitrogen fraction in excess of 9 per cent is to be regarded as an evidence of disturbed metabolism. While high values are found in all endocrine conditions and their incidence is frequent,† we regard the phenomenon as an indication of the influence of ductless glands on general metabolism rather than a pathognomic sign of endocrine malfunction. The data given above offer strong supporting evidence for this contention. While the average level is below the limit set for normality, in practically half of the cases it has been exceeded. The allocation of these cases to the several etiological groups is interesting.

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*Since the subject is shortly to be considered elsewhere no further discussion is necessary at this time.

†The endocrine relationships are as follows:

TABLE III-b

Gland	*Pituitary*	*Thyroid*	*Ovary*	*Adrenal*
Residual N_2, Av.	9.4%	10.3%	9.1%	9.3%
%=or> 9%	51	61	48	56

Only in subjects of thyroid and adrenal involvement does the incidence exceed significantly that of the non-endocrine subjects, although all of the glands exhibit averages above the normal limit.

TABLE III-c

Etiology of Non-Endocrine Cases Exhibiting High Urinary Residual Nitrogen.

Etiological Group	Total Cases	No. with High N_2	Per Cent
Primary Infections	53	27	51
(a) Secondary to other disease		9	
Psycho-Neurotic States	60	36	60
Lesions of Cent. Nerv. System	44	26	59
Epilepsy	9	7	78
Park. Syn. and Paral. Agit.	10	4	40
Syphilis	42	24	57
Diseases of Kidney	50	29	58
(a) Secondary to other disease		24	
Anaemia (prim. and sec.)	10	7	70
Leukaemia (myel. and lym.)	6	6	100
Tumors (mal. and benign)	12	8	67
Goiter, non-toxic[1]	8	4	50
Normal	18	0	0
		211	

NOTE—Total of 235 cases in 489 recorded.[2]

[1]Concerning the propriety of the inclusion of this group, see text.

[2]The remaining 24 cases were too widely scattered to possess any etiological significance.

The high incidence in epilepsy, leukaemia and the tumor group is striking though it exceeds, in degree only, several of the other groups which show a frquency of over one in every two cases. As an evidence of metabolic disturbance we feel the case established; as a differential diagnostic point it is wholly non-specific. Undoubtedly had this investigation extended to other morbid states, additional conditions would be included. It is perhaps important that the so-called diseases of metabolism

TABLE IV

BLOOD CHEMISTRY (AND SEROLOGY)

	High	Low	Average	Deviation	Per Cent
Non-Protein Nitrogen.....(mgm.)	128	11	32	> 35 mgm.	20
Urea Nitrogen.....(mgm.)	75	6	15	> 17 mgm.	20
Uric Acid.....(mgm.)	7.1	1.7	3.5	Net(1) = or > 4 mgm.	10
Creatinin.....(mgm.)	5.0	1.0	1.5	–	–
Residual Nitrogen.....(mgm.)	>50	< 5	15.2	–	–
Sugar.....(mgm.)	133	68	97	>120 mgm.	4
				< 80 mgm.	3
+Wassermann.....%			6		
+Kahn (presump.)....number			10		
+Spinal Fluid.....number			8		
+Schwartz-McNeil....number			1		

(1) All cases demonstrating Nephritis and Gout have been deleted.

are not represented in the group. The term "metabolism" is a comprehensive one and includes a myriad of interrelationships. A possible dominance of the nervous system might be deduced from these figures but the seeming relationship may be only an arithmetical artefact. Many thousands of diverse observations would be necessary to resolve the question with any measure of certainty.

As the precursor of the urine, the blood in its chemical aspects may next be considered.

Since renal disease plays a not inconspicuous part in this series, it is to be expected that high values will appear in the individual observations. Inspection of the superior limits shows values compatible with severe but not terminal nephritis. Twenty per cent show values for non-protein and urea nitrogen in excess of the conventional normal.

Significant from the differential standpoint is the relatively low incidence of high uric acid values. A high blood uric acid with relatively normal non-protein nitrogen has been observed in pituitary malfunctions, and in the proven absence of nephritis and gout may possess definite diagnostic value. The relative infrequency in the non-endocrine group enforces the observation.

Another significant feature is the small percentage of blood sugars falling outside the conventional normal limits. Further, the maximum individual deviations observed are of the order of ± 10 to 15 per cent, and those were recorded in single cases only. If the average values be taken for the several quantities, the entire picture is one of the most rigorous normality. Six per cent of the cases showed positive Wassermanns, confirmed in the ten most recent cases by a similar response to the Kahn presumptive test. Incidentally, the correlations in the series are complete.

In addition, eight other cases gave positive results, indicating neurosyphilis, in the examination of the spinal fluids. For obvious reasons, lumbar punctures were not a part of the invariable routine, but were performed wherever history, physical examination, or laboratory picture gave evidence of a possible specific condition. A few Schwartz-McNeil tests were made, giving a positive response in only one case. Of the forty-two cases in which syphilis was the primary condition, thirty-eight were confirmed by the positive serological findings, while in the remaining four the diagnosis was equally certain although treatment had obliterated the serum response.

The character and amounts of the several form elements of the blood is always important, and in not a few conditions determine the final diagnosis. Our own observations are assembled in Table V.

TABLE V

BLOOD MORPHOLOGY

General Examination		Amount	Differential Count[1]	Per Cent
Haemoglobin	High (%)	>100	P. M. N. Neurtophiles...Average	61
	Low (%)	15	% >75%	6
	Average (%)	87		
Erythrocytes	Average (10^6)	4.85	Lymphocytes...Average	31
			% >33%	43
Color Index		0.90	Eosinophiles...Average	2
			Net[2] % = or >3%	15
Leucocytes	Average[1] (10^3)	8.1	Endothelials...Average	6

[1] Omitting data of 6 cases of Leukaemia.
[2] Cases in which a non-endocrine cause of eosinophilia was demonstrated, have been deleted.

In compiling these averages, the few cases of primary anaemia have been included but, as is stated in the footnote, the cases of leukaemia were deleted from the leucocyte average. Typical observations in this group were 92,300 and 82,900 in two representative cases. The inclusion of these would change the average by nearly 10 per cent and render it by so much the less representative of the entire group. Taking the picture presented by the average values, the general impression is one of normality. The haemoglobin value is somewhat low, but the cases composing the group included many in which slight secondary anaemia is a common feature. This is also reflected in the red count.

The differential count, from its relative character, is perhaps somewhat more significant. The lymphocyte average is normal in contradistinction to that in the endocrine cases as shown in Table V-a.

TABLE V-a

Lymphocyte Count Averages.

Gland	Pituitary	Thyroid	Ovary	Adrenal
Lymphocyte %	36	37	35	37
%=or > 33%	59	60	56	50

While these values exceed those of the non-endocrine group, the differences are not great. Further, while the latter series averages less than the arbitrary "normal," nearly half of the cases in the group exceed this limit. An allocation of these cases to the several general diagnostic groups is presented in Table V-b.

TABLE V-b

Etiology of Non-Endocrine Cases with Lymphocytosis.

Etiological Group	Total Cases	Cases with Lymphocyt.	Per Cent
Primary Infections	53	26	49
(a) Infection (secondary)	..	10	..
Psychoneurotic States	60	36	60
Lesions of Cent. Nerv. System	44	19	43
(a) same, secondary	..	1	..
Epilepsy	9	2	22
Park. Syn. and Paral. Agit.	10	9	90
Syphilis	42	19	45
Diseases of Kidney	50	24	48
(a) same, secondary	..	26	..
Anaemia (primary)	8	5	63
(secondary)	2	0	0
Leukaemia (myel. and lymp.)	6	3	50
Tumors (mal. and benign)	12	3	25
Goiter (non-toxic)	8	3	38
Normal	18	0	0
		186	

NOTE—Total of 215 cases in 489 recorded. The remaining 29 cases were widely scattered.

The same general diagnostic groups are the representatives in this compilation as in that dealing with the high residual nitrogen. Further, in certain members the correlations are definite, as in the groups of infections, the mental and nervous disease group, and less strikingly in the syphilitic, cardio-renal groups, and those cases with lesions of the central nervous system. Equally, if not more significant are the divergences from parity. For example, the epileptic group shows a lymphocytosis far less frequently than a high residual nitrogen (78 per cent against 22 per cent), while the Parkinsonians (with Paralysis Agitans) exhibit more than double the incidence. Five in eight of the primary and neither of the two established secondary anaemia cases show it. There is a markedly lower occurrence of a lymphocytosis in the tumor group.

Whatever the exciting cause, it is obvious that two widely different mechanisms must be involved in the production of the two phenomena. As the matter contains certain possibilities, a still more detailed analysis may be permitted. Certain diagnostic groups have been shown to exhibit a practically equal incidence of the two aberrations, while in others there is a well defined difference. The relative frequency in which both are shown by the same individual has been determined.

TABLE V-c

Correlation of (a) High Residual Nitrogen
with
(b) Lymphocytosis in Non-Endocrine Group.[1]

Etiological Group	1 Total Cases	2 With a, b, or Both	3 With a+b	4 Per Cent + Cases	5 Per Cent All Cases
Infections	89	58	14	24	16
Psycho-Neurotic States	84	53	19	36	23
Lesions of Cent. Nerv. System	47	35	11	31	23
Epilepsy	10	7	2	29	20
Park. Syn. and Paral. Agit.	10	10	3	30	30
Syphilis	56	31	12	39	21
Diseases of Kidney	90	82	21	27	23
Anaemia	12	8	3	38	25
Leukaemia	6	6	3	50	50
Tumors	12	8	3	38	25
Goiter, non-toxic	8	6	1	17	13
Miscellaneous	..	..	10	..	..
			102		

[1]Both Primary and Secondary conditions are included.

In the various correlations, leukaemia leads easily, which is probably attributable to the fact that all cases show a high residual nitrogen. Obviously the correlation depends also on the proportion of the lymphatic type. Comparing frequency with incidence of one or the other condition (column 2 with 4), syphilis with low and anaemia and tumors with moderate frequency show a high correlation. On the other hand, the Parkinsonian (and Paralysis Agitans), kidney and goiter cases, show high incidence and

moderate or low correlation. Lesions of the central nervous system show a moderate frequency and a like correlation. The nervous and mental diseases with low, and epilepsy with moderate frequency show respectively moderate and low correlation. The infection group is consistently low throughout.

The authors offer no theory to explain these phenomena at this time but confine themselves to presenting the facts. One more comparison is suggestive, namely, the relative incidence in the several endocrine groups in comparison with the present diverse assembly.

Gland	N_2 Increased Lymph, Normal	N_2 Normal Lymph, Increased	Both Increased
Pituitary	19%	27%	33%
Thyroid	23%	22%	39%
Ovary	21%	28%	28%
Adrenal	31%	25%	25%
Total Endocrine[1]	20%	27%	33%
Non-Endocrine	27%	23%	21%

[1]Weighted for relative representation.

The greater measure of correlation in the endocrine group is apparent.

Reverting for a moment to Table V, it will be seen that not only is the average eosinophile value a normal one, but the percentage exhibiting eosinophilia is much less than with the endocrine group, particularly in the adrenal and pituitary cases.

A very definite influence on the respiratory metabolism is exercised by the members of the endocrine group. While the striking changes produced by aberrant thyroid function has tended to minimize the attention devoted to the other members of the concert, they all participate and determine certain highly characteristic deviations from the predicted normal. Improvement in accuracy and simplicity of determination of the magnitude has extended the study into numerous other fields, and it is recognized today that a variety of non-endocrine causes may produce deviations in the basal rate which equate in magnitude with those of endocrine origin. In any method of differential diagnosis employing basal metabolism tests, the non-endocrine become equally important with the endocrine cases and must be reckoned with primarily in any interpretation of data. Many of the early data relative to the basal rate in disease derives from duBois and his associates (7) at the Russell Sage Institute of Pathology, although Magnus Levy (8), beginning in 1894, established trends of deviation in a large number of disease conditions. Later workers have added much, and there is today a steadily growing and extensive literature which has been well reviewed in several recent monographs.*

The influences that have been observed can best be discussed after consideration of our own data. Because they are pertinent to the basal rate determinations, certain concomitant observations are likewise recorded.

*See among others Graefe (9), Boothby and Sandiford (10), McCann (11) and Selected Chapers in "Endocrinology and Metabolism" (12). See also the numerous publications of W. O. Atwater, F. G. Benedict, and their associates for many fundamental studies.

The observed rates vary from +49 per cent, which would equate with a moderate hyperthyroid condition, to —25 per cent, a level which might be associated with failure of any of the four principal endocrine glands (pituitary, thyroid, ovary, adrenal).*

On the other hand, the average of nearly half of the cases showing rates above prediction is only +7 per cent, while the somewhat larger group falling below the base line gives the same minus average. The net average deviates but 1 per cent from prediction. Further, 80 per cent of the cases fall within the conventional normal zone. With the exception of a few conditions which have been previously demonstrated to influence respiratory metabolism, the great majority of the cases fail to produce deviations which could confuse an endocrine diagnosis.

To specify the disturbing influences and indicate their extent, an analysis of our own data may be made and discussed with running comment on previously recorded observations. It should perhaps be empha-

TABLE VI

RESPIRATORY METABOLISM

Observation	Amount	Observation	Amount
Basal Metabolism		Blood Pressure	
Deviation.....High (%).....	+49(1)	Systolic.....Average (mm.)..	**124**
Low (%).....	−25	%=or>150 mm.....	11
+Average (%).....	**+ 7**	%=or<110 mm.....	24
%.....	44	Diastolic.....Average (mm.).	**73**
−Average (%).....	**− 7**	%=or>100 mm.....	6
%.....	56	%=or< 65 mm.....	27
Net Average.....	**− 1**		
% above +10%.....	6	Pulse Rate.....Av. (per min.)..	**77**
% between +10% and −9%.....	80	%=or>80.....	38
%=or below −10%.....	14	%=or<70.....	30
Alveolar CO_2.....Average (mm.)..	**39**	Respiration Rate.....Av. (per min.)..	**15**
% >35 mm.....	45	%=or>20.....	13
%=or<30 mm.....	7	%=or<10.....	9
		Temperature.....(deg. F.).....	**98.2**

(1) Lymphatic Leukaemia.

sized that the component cases of the groups here presented have been demonstrated to be free from endocrine complication. Where such exists, the case has been listed under the endocrine focus participating. To illustrate, a certain small percentage of arthritic cases have well established thyroid failure and improve on thyroid medication. Similarly, we have demonstrated that gall bladder (and liver) disease may accompany thyroid failure and seemingly be closely associated with it in a causal or resultant relationship. The coincidence of the two conditions has been remarked by others. The simultaneous presence of an endocrine malfunction, coincidently with a well-defined non-endocrine disease, may well account for some of the contradictory observations recorded in the literature.

Tuberculosis in its early stages at least and without a marked febrile condition, seemingly tends toward a normal or slightly depressed basal rate. This is in accord with the earlier reports. The high rates are usually

*For reasons earlier discussed, the pancreas has played no part in this study.

TABLE VI-a

Etiological Allocation of Basal Rates

Pathological Condition		High	Low	Basal Rates		Total	Group Average
Group	Detail			+	−		
Infections	Tuberculosis[1]	+12	−19	6 = + 5	11 = − 9	17 = − 4	
	Atrophic Rhinitis	+11	− 3	3 = + 9	1 = − 3	4 = + 6	
	Arthritis	+ 8	− 8	6 = + 3	12 = − 5	18 = − 2	− 3
	Gall Bladder Inf.	+ 6	−12	2 = + 4	6 = − 8	8 = − 5	
	Focal Infection	+ 6	−12	3 = + 2	2 = − 9	5 = − 2	
Psycho-Neurotic States	Neuroses	+12	− 8	10 = + 7	11 = − 5	21 = + 1	
	Psycho-Neuroses[2]	+10	−10	11 = + 5	12 = − 5	23 = − 1	− 1
	Psychoses	+17	−21[3]	7 = + 8	8 = − 8	15 = − 1	
Central Nervous System	Lesions of Central Nervous System	+19	−20[4]	19 = + 9	25 = − 7	44 = ± 0	± 0
	Epilepsy	+14	− 9	4 = + 8	5 = − 5	9 = + 1	
	Parkinsonian Syndrome and Paralysis Agitans	+105[5]	− 3	8 = +30[5]	2 = − 3	−	
Kidneys	Diseases of Kidneys	+15	−17	13 = + 7	9 = − 7	22 = + 1	± 0
	Cardio-Renal Disease	+20	−20	14 = + 7	14 = − 8	28 = − 1	
	Syphilis	+17	−23	20 = + 6	22 = −11	42 = − 3	− 3
Blood	Anaemia (primary)	+ 7	−25	5 = + 4	3 = −14	8 = − 3	−
	Leukaemia	+49	− 4[6]	5 = +31	1 = − 4	6 = +25	−
	Tumors	+14	−15	6 = + 7	5 = − 8	11 = ± 0[7]	− 1
	Non-Toxic Goiter	+10	−11	3 = + 4	5 = − 6	8 = − 2	
	Obesity	+ 8	−11	6 = + 3	6 = − 4	12 = − 1	− 1
	Asthma	+ 9	−10	3 = + 4	8 = − 6	11 = − 3	− 3

(1) Afebrile. Average Temperature = 98.4°.
(2) One case omitted (+29) where patient restless and value obviously too high.
(3) Marked malnutrition. Next low case −9.
(4) Brain Tumor.
(5) See text (6 cases = +11).
(6) During remission period. High rates observed later.
(7) Basal Rate not obtainable in one case.

but the expression of the influence of fever, as duBois has so clearly shown. Graefe's few severe cases would seem to offer an unexplained exception.

Uncomplicated arthritis apparently arising from infective processes is rigidly normal in this series. The low values which are occasionally recorded are possibly due to an endocrine element. The same is true for cholecystitis, although malnutrition may operate in this condition to lower the basal rate. The group which we have conventionally designated as "Infections" shows no evidence of significant departure from prediction.

In the next group of nervous and mental states two complications may arise. First, some cases presenting one or another of these conditions may have a definite endocrine complication which seemingly is causal (see paper on Thyroid in this series, l.c.). That the speculative practice of ascribing all mental disease to endocrine aberration is unwarranted, the cases listed above will prove. Again at the risk of over emphasis it may be said that the final diagnosis rests on a very complete clinical and laboratory study in which each observation is interpreted in the light of numerous others. The endocrine complicity is neither included nor excluded on the basis of a single test, and certainly not on that of a single opinion. If this current study of approximately two thousand cases (supported by nearly two thousand more since this compilation was begun) can be taken as warranting a tentative opinion, the percentage of psychotic cases which can be proven to derive from endocrine malfunction is not large. Equally, however, a definite number do demonstrate an endocrine etiology and this factor must be considered. The second complication is implicit in the nature of the case. Slight movement will exercise a wholly detrimental effect on the accuracy of the test, and nervous instability may determine muscular efforts too slight to produce gross movement but ample to vitiate the measurement. We have deleted two of our cases for this reason, and regard many of the retained values as probably somewhat above the truth. Due attention to this disturbing element and the education of the patient by repeated tests as a means of correcting it, will give fairly representative values. We feel, in the cases reported, that gross error has been eliminated.

So comprehensive a term as "lesions of the central nervous system" naturally embraces a wide variety of conditions. In some of the brain tumor cases the lowered rates were possibly attributable to pressure influencing the pituitary unfavorably. In one case which we were privileged to study and which gave all of the typical evidences of pituitary disease, autopsy demonstrated that the neoplasm localized outside of the gland but had produced a sufficient intracranial pressure seemingly to determine a typical pituitary dysfunction. The cases here listed gave no evidence of pituitary participation other than the possible influence on the basal rate. The group of epileptics is also normal, although in several cases degenerative changes had resulted from a long standing condition.

The group of Parkinsonians (including a few cases of paralysis agitans) are extremely interesting. Very high values were obtained in a few cases but we were fortunate enough to secure several in which the

syndrome was in its incipiency.* These cases showed values which were normal or, at the worst, but slightly above the normal level. This seems to confirm the opinion of Magnus Levy (13), although by no means controverting the later opinion of Graefe (14). In this connection, a case of paralysis agitans, observed in the course of another study, offers information of value. The patient, a man in the late fifties and with a very pronounced tremor, was studied at two-week intervals for a considerable period. His prevailing rate lay with surprising uniformity between +60 per cent and +70 per cent. At the time of one test in the middle of the series, it was noted that his tremor was perceptibly less, and on this day the rate dropped to +24 per cent. When next seen the tremor had resumed its wonted course and the rate was +64 per cent. A single observation of this character is interesting even though it cannot be regarded as decisive.

Our renal cases show the general normality that has been recorded by others. Edema was not a complication in this group. The cardio-renal group practically repeats the kidney observations, although the extreme limits are slightly wider. Individual cases, however, may well have some slight superimposed effect (low protein diet, for example, in a considerable number of these cases) which will in summation exceed the normal limits. We feel that this explains our own cases showing a hypofunctional level. The actual numerical values of the low readings are more significant than the high, for reasons that have already been discussed.

The syphilitic cases show a definite downward tendency. Twenty-two cases average —11 per cent, and in this group are several with rates of about —20 per cent. When taken in conjunction with the influence on carbohydrate metabolism frequently exercised by this disease, it is evident that syphilis may simulate endocrine disease in some measure. While the serological tests should preclude frequent grave error, the necessity for their performance is patent.

Primary anaemia has severally been recorded as ranging from about —20 per cent to +30 per cent, both extremes suggesting a possible endocrine involvement. In our own very small group but one case falls outside relative normality, and as this is to be discussed later, comment may be postponed.

The tumors, both malignant and benign, fall reasonably within the normal zone. Boothby and Sandiford report one case of Hodgkin's disease with a rate above +20 per cent. Our two cases gave readings of, respectively, +3 and —15 per cent.

The basal rates of the non-toxic goiter cases offer one definite warrant for their inclusion in the non-endocrine group. Physiological obesity, as was earlier shown by Means (15) exercises no detectable influence on the basal rate.† The asthma cases are recorded as the condition is, from time to time, referred to an endocrine origin. The present group gives no evidence of any hormonic influence.

*The authors wish to express their thanks to Dr. N. H. Garrick for his interest and courtesy in securing these cases for us.

†The cases here listed averaged 101.2 kgm. and 59 per cent above predicted weight.

Reverting to Table VI, it will be noted that while the averages for the Blood Pressure are entirely normal, an appreciable percentage (about one-fourth) show hypotensive levels which might suggest endocrine disease. The Pulse Rates show nearly 70 per cent outside of the range of from 70 to 80. The other findings are essentially normal.

Alveolar carbon dioxide exhibits a normal average, nearly half the cases above the conventional lower limit of normality and but 7 per cent showing a tension suggestive of acidosis. With the number of kidney cases in which a retention acidosis is possible, the value observed is reasonable. While the general picture is a normal one, enough has been shown to indicate that individual cases may far exceed normal limits, and by a fortuitous combination suggest an endocrine malfunction, the non-existence of which can be demonstrated only by a comprehensive study.

The sugar (galactose) tolerance is the sole remaining laboratory test permitting presentation in tabular form.

TABLE VII

GALACTOSE TOLERANCE

Observation	Unit	Male	Female	
Tolerance Dose..... High.....	gms.	40	40	
Low.....	gms.	5	5	
				Summary
% above Normal.....	%	3	0	
Average Deviation.....	%	+33	—	% > Normal..... 1
				% = Normal..... 41
% equal Normal.....	%	37	43	% < Normal..... 58
% below Normal.....	%	60	57	Av. Deviation(1) >N... +33
Average Deviation.....	%	−47	−43	Av. Deviation(1) <N... −45

(1) Not weighted for numbers.

The test is one of great differential significance, as there is not only an intrinsic sex difference, but each of the important endocrine glands exercises a definite and characteristic influence on the amount of the sugar capable of utilization. In the table given above, slightly less than 40 per cent of the cases are considered. The data here reported are derived from the routine work of a consulting diagnostic service. The sugar test, which requires two or three days for performance, is performed only when its indications are essential for the establishment of a diagnosis.

Of the cases examined, less than half showed a normal tolerance.* Only two cases showed a tolerance above normal, and those were both advanced cases of chronic interstitial nephritis. Lessened permeability of the kidney rather than heightened carbohydrate tolerance is patently the cause of this observation.

*As has been stated in the previous papers, the male tolerance is unvarying and at 30 grams. The female, on the other hand, is normal with 20 grams in the prepubertal period, passes during puberty by degrees to 40, the normal adult level, and at the menopause may maintain the adult 40 or more usually, or recede to 30 grams. Pregnancy lowers the tolerance first to 30 and later to 20 with restoration to the normal adult level with the resumption of sexual rest. For this reason, tolerances are expressed in percentage deviation from the individual norm.

The allocation of the remaining one hundred and twelve cases showing a lowered tolerance bears directly on the thesis.

Of parallel observations but a few need be mentioned. Bauer (16) first suggested the use of galactose as the basis of a tolerance test, applying it to liver conditions. His primary contribution was followed by numerous studies, which have been summarized by Wörner (17). Later studies have supplemented and confirmed the earlier opinions. Offenbacher (18) has demonstrated that galactose and levulose are both influenced by liver integrity, while glucose, on the other hand, seemingly is not. Bauer, in a later paper (19), records observations in cases of syphilis and of malignant neoplasm, using a uniform test meal of 40 grams. As an elimination of less than 3 grams was regarded by him as a negative response, his conclusion of normality in these conditions is erroneous. The writer's own

TABLE VIII

Etiological Allocation of Cases with Abnormal Tolerance.
112 Cases with Lowered Tolerance

Group	
Central Nervous System[1]	43[2]
Psycho-Neurotic States[1]	15
Syphilis	15
Primary Anaemia	7
Leukaemia	4
Tumors (malignant)	3
Asthma (Adrenalin med.)	2
Gall Bladder (Liver)	7
Hypertension	4
Total	100

NOTE—Of the 12 remaining cases, all show a depression of only 10 grams.
Two cases with increased Tolerance (males at 40) had advanced Chronic Interstitial Nephritis.

observations show that a significant percentage of syphilities show a definitely lowered tolerance, and similar findings in malignant neoplasms are confirmed, among others, by Friedenwald and Gross (20) and Langston (21). The observations of Lorenz (22) would seem to indicate a lowered tolerance in certain psychotic states, although Barrett and Serre (23), in dementia praecox, were unable to demonstrate any consistent abnormality in sugar tolerance. Hirose (24), Strauss (25), Wagner (26), and others, have noted depressed tolerance for galactose in the neuroses. O'Hare (27) found abnormal tolerance in one-half of a series of hypertensive cases. Davidson and Allen (28) have shown a lowered tolerance in head injuries, and Kasanin and Garfield (29) observed decreased tolerance, associated with encephalitis, in adults, although the opposite obtained with children.* Richard Bauer (30), using 40 grams of galactose as a test meal and regarding an elimination of less than 2 grams as negative, could find no influ-

*In many of the papers cited above, tolerance was determined by the shape of the sugar curve. Comment has already been made upon the lack of quantitative significance of the single sugar curve. It may be regarded, however, as offering some qualitative evidence of the relationship of the exciting dose to the individual tolerance.

[1]See Table I for composing members.

[2]Percentages are not given as all of the cases in a group did not receive the sugar test.

ence on the tolerance in primary anaemia. With the wide range of conditions listed in which a lowered tolerance is a possible or even a probable observation, it is obvious that the test, while of great differential value, requires a variety of supplementary tests for its proper interpretation.

It will be remembered from Table III, that 9 per cent (45 cases) showed glycosuria. While the metabolism of glucose and of galactose, in some measure at least, bespeak different mechanisms, the lowered tolerance for galactose offers a possible explanation of the glycosurias observed. The whole question of non-diabetic glycosuria* is implied in the observations of this and the several endocrine series. Seemingly many agencies operate to lessen the power of the body to utilize carbohydrate. While pancreatic diabetes is the prototype, there are many other conditions producing the same end result but engendered by wholly different causes and operating under wholly different laws. The end result of glucose in the urine is the only point they have in common.

PART II.

CLINICAL SECTION

Introduction. Although the differential diagnosis of endocrine and non-endocrine conditions usually depends upon laboratory findings for its confirmation, the attempt of the clinician should always be toward simplification, since in many instances there is neither time, money, nor facilities for an elaborate study of the patient presenting an obscure disease picture. It is under such conditions that so much "experimental" endocrine therapy is employed, to the detriment of that branch of medicine and often to the patient. Therefore the present analysis was undertaken to determine what symptoms and signs are significant in separating endocrine from non-endocrine conditions, and to what extent that differentiation may be made without the aid of laboratory examinations.

It is well perhaps to state at the outset that so far as differential diagnosis is concerned, the non-endocrine conditions which have come to us for metabolism studies may be separated into two groups: namely, those in which the history and a careful physical examination disclose a typical picture, and those in which the history does not indite one organ or system and the physical examination is significant, largely because it affords only "negative" or non-specific evidence. In the former group, laboratory examinations may furnish corroborative evidence in regard to diagnosis, and valuable aid in treatment, but they are not essential for the identification of the disease present; while in the latter group, laboratory tests must be relied upon, in the present state of our knowledge, to disclose the facts by means of which the diagnosis is reached. For example, disease of the heart, or circulatory system, can almost always be satisfactorily diagnosed by means of the patient's story and the clinician's examination, and while electrocardiograms, blood pressure measurements and radiograms of the

*A paper is shortly to appear treating this matter in detail.

heart may furnish comforting assurance that the diagnosis is correct, they seldom modify it or the treatment essentially. In contrast, in primary anaemia, diabetes, asthma, syphilis often, and disorders of metabolism practically always, the laboratory evidence is necessary if the diagnosis is to be certain and treatment effective.

In this section, therefore, emphasis is placed on diseases of the latter group, since they are the ones most often confounded with one another. It is not often, in our experience, that infectious endocarditis and thyrotoxicosis are confused; the difficulty, as judged by the character of the patients referred to us, lies in separating neuroses of neurogenic origin from those secondary to metabolic disturbances, or in recognizing tertiary syphilis, early lesions of the central nervous system, anaemias and leukaemias as the cause of the patient's condition. The diseases which are most frequently confused with endocrine disorders may be found in table (I) (v. s.) which comprises a diagnostic grouping of the patients examined by us who showed no convincing evidence of endocrine disorder but in whom evidence of other functional disturbance or organic disease was found.

The table shows that the principal non-endocrine conditions encountered were, in their order of incidence, lesions of the central nervous system, cardiovascular diseases, psychoneuroses, deafness, chronic infections, and syphilis. The high incidence of vascular disease and deafness in this group is artificial, due to factors already pointed out.

A more exhaustive analysis of the diagnostic groups remaining serves to show why they are frequently mistaken for endocrine disturbances. Thus, of the central nervous system lesions, the greatest number were post-meningitic or post-encephalitic arrests of development, with a lesser number of epileptics and patients with the Parkinsonian syndrome. The differentiation between post-meningitic or post-encephalitic arrests of development and those due to mild thyroid failure, is from clinical evidence alone, often impossible, and since the former conditions are almost irremediable and the latter responds dramatically to treatment, it is only proper to give the patient the benefit of any existing doubt, and to determine, by means of such laboratory investigations as are necessary which condition really exists. So far as epilepsy and paralysis agitans are concerned, their frequent occurrence in our series is due not to mistaken initial diagnoses but to a commendable effort to detect, if possible, a curable cause for the symptom complex presented. In epilepsy, our studies have occasionally brought to light some associated disturbance of metabolism, the correction of which has resulted in an arrest of the convulsions, while in the case of Parkinson's syndrome they have served to disprove the theory that the condition is in some way due to "hypoparathyroidism."

Under the heading "psychoneuroses" are included neuroses and psychoses as well as true psychoneuroses. Whether or not the patients were correctly allocated to their proper sub-group, it is a significant fact that the symptoms were no more varied or severe in these "non-endocrine" patients than in those showing incontrovertible evidence of associated endocrine dis-

turbance (1, 2). We have been forced to conclude that every patient exhibiting symptoms of neurosis, psychosis or psychoneurosis deserves a careful medical endocrine study before the condition is ascribed to "neurogenic" or psychogenic causes. We do not wish to be understood as ascribing every neurosis or psychosis to disturbed endocrine function: but we do wish to emphasize the point that only by careful metabolic studies can such a condition, either associated or causal, be eliminated in case of any given patient.

In the group of the chronic infections, tuberculosis heads the list. Little comment is needed on this point. The difficulty of differentiating incipient phythisis from thyrotoxicosis has been pointed out by many writers, but it needs repetition in these days of diagnosis by means of a single basal metabolic rate to the exclusion of repeated physical examinations. It is perhaps significant that focal infections, not associated with disturbed metabolism, are so rare in our series. Attention has already been called in our papers on thyroid ovarian and pituitary disturbances, to the high incidence of focal infections in association with those conditions: the material presented here tends to support by its negative character our suggestion that focal infection certainly, at times, produces its deleterious effects via the endocrine system.

The presence of a large percentage of syphilitics in a series of patients suspected of endocrine malfunction is to be expected, and serves to illustrate the protean character of lues. It serves also to make clear the necessity for serological tests on all patients suffering from obscure conditions.

One other group of patients deserves comment here, that labeled in the table "disorders of metabolism." Though less important, numerically, it comprises two conditions often wrongly charged against faulty endocrine function, "malnutrition" meaning underweight, and obesity. Our studies of these patients confirm the opinion of other writers that in by no means all obese patients can a metabolic disturbance be demonstrated and to a certain extent controverts the theory frequently encountered that a pluriglandular preparation is a good "tonic" for any individual who is underweight.

To summarize briefly the conclusions to be drawn from Table I, it may be said that, in considering the possibility of disturbed endocrine function in any patient, tuberculosis, syphilis, sequellae of meningeal infections, and "idiopathic" malnutrition and obesity must be ruled out by adequate objective evidence, while the possibility of disturbed endocrine function as a contributing or causal factor exists in any case of epilepsy, neurosis or psychosis, a possibility demanding adequate objective evidence for its proper evaluation.

An analysis of the histories and physical examinations of patients in the non-endocrine group justifies our emphasis upon the importance of the clinical examination of the patient, since it reveals certain facts which are of considerable help in separating, at least tentatively, the "endocrine" from the "non-endocrine" individual. This, although we believe that in

the majority of instances the clinical evidence must be substantiated by correlated laboratory tests before the examiner can properly treat the patient with an endocrine preparation. It must be recognized that many individuals can be spared the expense and bother of metabolism studies if the examiner gives sufficient time and thought to the results of his personal examination. A brief discussion of the most important clinical findings in this series is therefore necessary.

TABLE IX

FAMILY HISTORY

Malignant	19.6%
Diabetes	7.0%
Thyroid Disease	3.0%
Tuberculosis	18.0%
Mental Disease	8.0%
Epilepsy	0.6%
Venereal Disease	1.0%
Blood Diseases	1.8%
Cardio-Vascular Diseases	13.8%
Disease similar to that of Patient	19.2%

Inheritance. The importance of inheritance in determining a patient's tendency toward certain diseases is still a matter of argument. With the growth of laboratory methods of diagnosis the "family history" was at one time almost disregarded, but more recent opinion seems likely to give it a place of considerable importance as an aid to diagnosis. Familial tendency to endocrine disorders is generally recognized, and our own studies (g. v.) furnish evidence in support of this idea. They also indicate that this familial tendency is more marked in endocrine than in non-endocrine diseases, since in the former there is a "positive" family history in approximately 40 per cent of the cases, while in only 19 per cent of the latter group was there a history of a near relative who suffered from the same disease as did the patient. These figures are not quite comparable since the term "endocrine disorders" embraces a large number of clinical conditions, but the preponderance indicates that careful inquiry into the patient's family history is likely to furnish evidence valuable enough to justify the effort involved. It should be pointed out, however, that the inheritance is not always specific. The fact that a parent or sibling has thyroid disease is no evidence that the patient's symptoms are due to abnormal function of that gland, but does furnish strong presumptive evidence that they may be associated with some endocrine disorder, if no organic pathology is found to explain them.

Sex. As regards this factor, our figures do not support the thesis that the female sex is peculiarly liable to endocrine diseases. Practically all of the gonad subjects (95 per cent), 73 per cent of our patients with thyroid disease and 60 per cent of those with pituitary disorders were females, but the possible significance of these figures is nullified by the fact that 63 per cent of our patients with non-endocrine disorders were also

females. The only conclusion justified by these findings is that, for reasons not pertinent to this study, women predominate in hospital clinics, and that in our material, the percentage of males with endocrinopathies was not significantly smaller than that with non-endocrine disease. We believe that endocrine disturbances are more frequently encountered in men than is generally supposed.

TABLE X

Diagnostic Group	Age Years 1-10	11-20	21-30	31-40	41-50	51-60	over 60	Aver.
Infections	0	6	10	14	15	11	0	38
Psycho-Neuroses	1	3	22	14	11	6	3	36
Lesions of Cent. Nervous System	8	18	26	12	11	4	3	29
Metabolism	1	6	9	8	5	1	5	35
Cardio-Vascular	1	6	9	11	11	8	15	44
Blood	0	2	2	2	2	6	3	46
Tumors	1	0	8	2	5	1	3	37
Syphilis	2	9	6	11	7	4	4	35
Eye	0	0	1	0	1	1	2	50
Ear	1	8	22	12	10	3	1	33
Skin	1	3	7	2	0	4	0	31
Gastro-Intestinal	0	1	3	1	5	0	0	34
Pelvic	0	0	2	3	0	1	0	34
Asthma	0	2	0	1	4	2	2	44
Misc.	0	0	0	0	1	1	0	49
Normal	2	2	5	4	3	1	1	30
Total	18	66	132	97	91	54	42	36
Per Cent	3.6	13.6	26.4	19.4	18.2	10.8	8.4	

Age. On the basis of division by decades, there is no significant difference in the age incidence of endocrine disturbances and those non-endocrine conditions which are most frequently confused with them. All

TABLE XI

Marital History and Fecundity

Diagnostic Group	Married No.	%	Dur. Av.	Conceptions	Children	Miscarriages	Abortions	Infertile No.	%
Infections	32	57	16	74	63	11	0	5	16
Psycho-Neuroses	31	52	13	60	44	11	5	9	29
Cent. Nerv. System	30	37	14	60	47	12	1	12	40
Metabolism	17	49	19	48	28	19	1	5	29
Cardio-Vascular	39	64	22	125	99	15	11	5	13
Blood	12	71	25	31	24	7	0	3	25
Tumors	10	50	12	12	10	2	0	4	40
Syphilis	21	49	17	68	52*	15	1	9	43
Eye	4	80	31	15	14	1	0	0	0
Ear	18	32	13	30	27	3	0	5	28
Skin	3	18	17	9	8	1	0	0	0
Gastro-Intestinal	5	50	9	10	8	1	1	1	20
Pelvic	5	83	12	11	9	2	0	2	40
Asthma	6	55	23	14	10	4	0	2	33
Intoxications	2	100	23	8	4	1	3	0	0
Normal	7	39	12	18†	9†	5	1	2	29

*One with 15 and one with 10; remaining 19 had only 27 children.
†Three pregnant.

are characteristically diseases of adolescence and early adult life, though no age period is free from them. A few of the non-endocrine groups such as that of cardiovascular disease show some deviation but are not those in which confusion is most likely to occur.

Fertility. A study of sterility in "endocrine" and "non-endocrine" patients brings to light some interesting facts. Of our "non-endocrine" patients 26 per cent of the matings were infertile, as compared with 39 per cent in the thyroid, 36 per cent in the pituitary and 41 per cent in the ovarian group, evidence that a history of sterility is an important suggestion of endocrine disturbance. Further analysis of the non-endocrine group shows that the conditions most frequently associated with sterility include two which are difficult to differentiate from endocrine disorder, syphilis with 43 per cent and lesions of the central nervous system, with 40 per cent infertile. The only other conditions showing the same incidence of putative sterility are pelvic disease (40 per cent), tumors, benign and malignant (40 per cent) and asthma (33 per cent). The coincidence of pelvic disease and syphilis with sterility is well known and easily understood; that of asthma, tumors and central nervous disease we believe has not been previously recognized, and we have no explanation to offer for our findings. From the point of view of internist, obstetrician and gynecologist, however, it is important to realize that in searching for the cause of a sterile mating, a possible endocrine factor must be considered as important as any other single cause.

TABLE XII

CATAMENIA

A. Onset	Before 12 22	12-14 212	After 14 65	Total 299
B. Period	Diminished Flow	Normal	Increased	Total
Irregular 85				
Diminished	7	16	11	34
Both	2	4	3	9
Increased	15	17	10	42
Total	24	37	24	85
Regular 214	41	138	35	214
Grand Total	65	175	59	...

Catamenia. Seventy per cent of our female patients in the non-endocrine group began to menstruate between their twelfth and fourteenth years, as compared with 45 per cent of the "thyroid group" and 65 per cent of the "pituitary group." In other words, non-endocrine diseases do not, in the majority of girls, cause significant delay of the menarche; but do cause such delay in over half of those with thyroid failure and in approximately one-third of those with disturbed pituitary function. These figures naturally derive from groups composed, in significant measure of women whose endocrinopathy was present during the years of maturation. In certain much larger series compiled by one of us (A. W. R.) the differences are less striking, but in each of these were a large number of women

whose history and physical evidences indicate an inception of the endocrine condition, years after the transition to maturity had taken place. In these larger groups, the ovarian cases show by far the largest proportion of women maturing within conventional normal limits, a possible indirect evidence either of the lesser part played by the gonad before maturity or equally to be interpreted as a lessened incidence of lowered glandular activity in the prepubertal years. Though the absolute figures differ, practically the same ratios hold for physical development in general, as indicated by abnormal weight and height, while the incidence of delayed mental development was practically the same in endocrine and non-endocrine conditions. As far as our evidence goes, arrested or delayed mental development is as often due to meningeal infections or birth trauma as to disturbed function of the glands of internal secretion. Over 70 per cent of the non-endocrine group show regularity of the menses, while the endocrine groups show a definitely lower incidence. The pituitary and ovarian cases show a tendency toward a lengthened interval while the thyroid group contains from four to five times as many women with complete irregularity as do any of the others.

The normal amount of the flow is somewhat elastic in its definition. Making due allowance for this fact, however, we find that while all of the groups show 50 per cent or more falling inside conventional limits, the division of the remainder between flow that is "scanty" and that which is "profuse" approximates a parity in every instance.

TABLE XIII

AGE OF ONSET OF CHIEF COMPLAINT

Period	Incidence			
	Non-Endocrine	Pituitary	Thyroid	Gonad
0-10	14%	2%	2%	9%
11-20	24%	30%	19%	32%
21-30	20%	22%	20%	31%
31-40	18%	17%	17%	16%
41-50	13%	20%	17%	7%
51-60	7%	8%	18%	3%
Over 60	4%	1%	7%	2%

DURATION, NON-ENDOCRINE

Less than 1 year	12.8%
From 1 to 5 years	43.4%
From 6 to 10 years	20.8%
Over 10 years	23.0%

Age of Onset and Duration of Chief Complaint. The statements from which the above data derive are a somewhat uncertain quantity in which a subjective element is or may be dominant. For example, the high degree of incidence shown in the first three decades in the ovarian cases may be a real datum or no more than an expression of the ego centricity of the sufferers from this particular disorder. Barring the relatively high value for the incidence during the first decade in the patients forming the non-

endocrine group, the major sections show a definite degree of correlation with those of the pituitary series. The gonad cases concentrate in the first three decades, while those patients presenting thyroid disease show a substantially constant recognition with low incidence only in the first and last stadia. In the light of the subjective element, it is hard to say how meaningful these figures may be. With the large percentage of normal catamenial histories in the ovarian group, the fact that two-fifths of them date their chief complaint from the first two decades, engenders a certain scepticism. The 14 per cent in the first decade of the non-endocrine cases undoubtedly arises in the large number of young patients with disorders

TABLE XIV

PAST HISTORY

Measles	83.8%
Mumps	48.2%
Chicken Pox	47.4%
Whooping Cough	59.4%
Scartlet Fever	26.2%
Diphtheria	16.6%
Typhoid	9.0%
Malaria	3.4%
Pneumonia	13.6%
Influenza	29.8%
Rheumatic Fever	3.2%
Arthritis	5.4%
Tonsil or Sinus, Infections	9.8%
Venereal Infections	7.8%
Nervous Diseases	3.0%
Encephalitis	3.4%
Renal Disease (acute)	1.2%

OPERATIONS

Tonsil and Adenoids		35.4%
Sinuses		3.0%
Infected Glands		4.6%
Eyes		3.6%
Nose		10.0%
Hernia		2.0%
Appendix		20.4%
Gastro-Intestinal		
Ulcers, etc.	2.2	
Gall Bladder	3.0	8.4%
Haemorrhoids.	3.2	
Tumors		3.8%
Pelvic		
Dilatation and Curettage	12.3	
Repair and Suspension	5.4	
Ovariectomy (one)	6.0	28.8%
Hysterectomy	3.8	
Caesarian Section	1.3	
Joint and Spine		5.4%

affecting the nervous system who were referred for the possible existence of a causal endocrine factor. This magnitude compared with the proportion of children in the pituitary and thyroid groups may offer a first rough approximation of the relative causation of physical or mental retardations.

The period of duration in the non-endocrine group does not differ substantially from our records in the endocrinopathies. This factor, like the

TABLE XV

COMPLAINTS

	Chief (as given by patient)	Combined Primary and Secondary
Headache	10.2%	57.6%
Vertigo	4.2%	30.0%
Fatigue	24.0%	36.8%
Faintness	3.4%	10.6%
Convulsions	4.2%	5.6%
Nervousness	9.6%	27.4%
Pain	16.0%	30.8%
Paralyses	3.6%	
Tremors	2.2%	
Mental Disturbances	5.0%	
Underweight	2.0%	
Overweight	5.8%	
Disturbances of the		
Eye	4.4%	
Glasses		55.4%
Pain		8.4%
Poor vision		16.2%
Visual aberrations		13.6%
Ear	14.0%	
Ache		11.4%
Deafness		28.6%
Tinnitus		17.6%
Nose	1.0%	
Colds (frequent)		22.2%
Catarrh (chronic)		7.0%
Epistaxis		7.0%
Discharge		5.4%
Obstruction		9.0%
Mouth (canker)		4.0%
Teeth		
Poor		18.2%
All extracted		10.4%
Throat		
Sore (frequent)		30.0%
Cardio-Respiratory System	5.6%	
Dyspnoea		35.2%
Palpitation		28.0%
Pain		17.4%
Cough		19.8%
Cardio-Vascular System	11.8%	
Gastro-Intestinal System	11.6%	
Nausea		21.4%
Vomiting		18.2%
Pain		15.8%
Jaundice		6.6%
Constipation		41.2%
Diarrhoea		4.0%
Poor Appetite		31.4%
Genito-Urinary System	2.8%	
Frequency		15.2%
Nocturia		19.8%
Urgency		5.2%
Dysuria		7.8%
Menstrual Function	6.0%	
Delayed Onset		21.7%
Irregularity		28.3%
Dysmenorrhoea		24.7%
Skin	4.6%	
Arthritis	6.4%	
Paraesthesias		17.6%
Ataxia		3.8%

age of onset, is influenced unduly by non-controllable influences. We offer them as the opinions which they are, not as facts.

Previous Illnesses. The one outstanding feature in this table is the significantly greater incidence of tonsillar infection in the endocrine than in the non-endocrine group. Judged by the same standards, the former showed about 75 per cent with convincing evidence of present or past tonsillar infection, the latter, 45 per cent. We have called attention to the possible relation of chronic tonsillar infection to endocrine disease in previous papers (2) but the findings become doubly significant in the light of our present records. It is probably also significant that while the number of tonsillectomies previously performed was not significantly different in the two main groups, the incidence of unrecognized tonsillar infection was much greater in those with endocrine disturbance than in that with non-endocrine disease. At first thought this findings may seem paradoxical, but we believe that the explanation is that constant absorption from the unrecognized chronic tonsillar infection may be a potent cause of deranged endocrine function in any individual with an inherited predisposition of those organs. As a corollary, we believe that failure of the patient's general condition to improve following removal of definitely infected tonsils in every instance should raise the suspicion of a residual endocrine disturbance.

No other diseases in the patients' past histories show any particularly significant variation in incidence in the various groups studied; in fact, the percentage of occurrence of illness other than focal infection is almost identical for endocrine and non-endocrine groups.

Present Illness. Exhaustion. As has been pointed out in a previous paper, the characteristic symptom of thyroid disturbance is exhaustion or easy fatigability, and in this particular it differs from other endocrine and from the non-endocrine group in striking fashion. Fifty-nine per cent of our patients with thyroid disorder gave abnormal fatigue as their chief complaint, and it was mentioned as a marked symptom by an additional 21 per cent. The only other group in which it occurs in anything like such proportions is that of Addison's disease, and in this the condition is more properly described as asthenia, since there is a sense of physical weakness rather than the loss of energy which characterizes thyroid disorders. This energy deficiency was a chief complaint in 36 per cent of both the pituitary and ovarian groups, but in only 24 per cent of our non-endocrine patients, and was mentioned as an important symptom by only 13 per cent more. There are, however, certain sub-groups among the non-endocrine conditions in which the incidence of exhaustion approaches that of the thyroid diseases. These are the nervous disorders, neuroses, psychoses and psychoneuroses and the anaemias. These latter conditions indeed offer the greatest difficulty of differentiation from the endocrine groups, and correct diagnosis demands great care in evaluating clinical signs and laboratory findings. The presence of an anaemia, for example, does not rule out thyroid hypofunction, since the former is often due to

the latter; nor does a moderate depression of basal metabolism in a neurotic patient prove the existence of an endocrine disorder. It may be, and in a significant number of our patients was, due to nitrogen starvation. Likewise exhaustion may be caused as surely by emotional conflict as by metabolic deficiency, so that it often requires nice judgment and all the differentiating evidence available to determine whether a given patient is exhausted and nervously unstable because of a metabolic error, or from an emotional state which has as one of its results an insufficient food intake.

Abnormal Weight. There is a widespread tendency at present to connect overweight with endocrine disturbance, and to overlook its possible relation to underweight. The theory that overweight is due to hypofunction of some gland of internal secretion has received enthusiastic support from patients wishing to reduce, as it seems to offer them a method of accomplishing their purpose without self-denial. The result has been the injudicious use of thyroid extract or pluriglandular preparations as an adjunct to, or substitute for, dietary restrictions—a practice with dangerous possibilities. As has been pointed out by one of us (31), if the basal metabolism is normal thyroid extract reduces weight only when it produces toxic effects. Furthermore, our figures, and studies by others (32), do not indicate that overweight is in any sense pathognomonic of endocrine disorders. Only in disturbances of pituitary function is there found an exception to this rule. In the thyroid group obesity was the chief complaint in 8 per cent; in the ovarian, 10 per cent; as contrasted with 6 per cent of the non-endocrine patients, an entirely insignificant difference. The subjective character of such a chief complaint as obesity is emphasized from the following.

TABLE XV-a

Gland	Thyroid	Gonad
Per cent above predicted weight	60	51
Average overweight	+27%	+22%
Obesity as chief complaint	8%	10%

In these same groups, significant underweight was nearly as common as overweight. In short, our studies lend no support to the use of endocrine preparations in the treatment of obesity, as such, and rob it of any valuable significance in the differential diagnosis of endocrine and non-endocrine disorders.

Headache, of more than occasional frequency, was the chief complaint in 10 per cent of this series, and was about equally distributed among the various subgroups. As a definite symptom its occurrence was slightly greater among the non-endocrine than in any of the endocrine groups, a fact which is of significance in indicating the variety of factors causing this symptom and in minimizing its diagnostic significance. There is, however, some suggestion that headaches of the true migrainous type are

more frequently associated with endocrine disturbances than with organic disease.

Nervous Instability. "Nervousness" was the presenting symptom in 9 per cent of the group under discussion, in 8 per cent of the thyroid disturbances, and in none of the patients with pituitary disorders. In the ovarian cases it was frequently mentioned but usually as a secondary matter. It is a striking fact that nervous instability, so characteristic of lowered ovarian function, as possibly evidenced during the menopause and, in a different manner, in thyroid disorders, is conspicuous by its absence in the patients with pituitary disturbance. No explanation of the fact is at present available, and the presence or absence of "nervousness" is hardly a dependable differential symptom. It may be stated, however, that its presence as a definite symptom should logically raise the question of an underlying metabolic error as its cause.

Vertigo was not a frequent chief complaint in our "non-endocrine" patients, but demands discussion because of its serious import when it is an outstanding symptom. Drury's recent paper (33) discusses it in detail but it needs to be emphasized that from the internist's point of view, vertigo demands a careful search for organic disease of the central nervous system as the first step in the diagnosis. To this end, ability to use the ophthalmoscope and a reasonable experience in interpreting its findings, is essential to every internist and general practitioner.

As compared with our endocrine patients, the incidence of vertigo as a presenting symptom is greater in the pituitary group and not significantly different in any of the others. As a definite but secondary symptom it is surprisingly frequent in thyroid disturbances, and in them, was occasionally so severe as to simulate closely an intracranial tumor. In the ovarian group, its incidence was trivial. Neither the character nor severity of a vertigo, therefore, is sufficient to define its cause in all cases, and the possibility of an endocrine etiology must always be kept in mind while examining a patient with that complaint. Such a possibility should not, however, be entertained until lesions of the central nervous system have been rigorously ruled out.

Menstrual Disturbances were not frequent among our "non-endocrine" patients, occurring in only 6 per cent of this series, although from 25 to 30 per cent reported dysmenorrhoea and irregularity. These figures are in striking contrast to those for the thyroid and pituitary groups, in which the incidence was 59 and 54 per cent, respectively, while the ovarian cases head the list with 14 per cent presenting this condition as a chief complaint and show, in addition, 42 per cent with irregularity and 68 per cent with dysmenorrhoea. Excepting demonstrable pelvic disease, the only non-endocrine diseases frequently associated with disturbed menstruation are tuberculosis, the anaemias and leukaemias, conditions which, as we have already pointed out, often closely simulate endocrine disorders. If these conditions be certainly eliminated, a study of endocrine function is indicated in any patient with disturbed menstruation, a fact emphasized

by Graves (34) and others. In the absence of definite pelvic disease, surgical treatment for menstrual disorder is justified only when a possible endocrine disturbance has been eliminated—not by one "basal" metabolism test, but by a careful survey of general and special metabolism, a fact not yet sufficiently appreciated by the medical profession as a whole.

TABLE XVI

PHYSICAL EXAMINATION

Development		
Good	70.4%	
Fair	21.4%	
Poor	8.2%	
Nutrition		
Good (normal)	35.8%	
Overweight	23.6%	
Underweight	40.6%	
Skull Abnormalities		9.0%
Hair		
Scant on Vertex	12.6%	
Excess on Body	12.8%	
Abnormal Pubic Distribution	4.8%	
Eyes		
Pupillary Abnormality	7.2%	
Abnormal Reflexes	9.6%	
Strabismus	4.0%	
Nystagmus	1.6%	
Exophthalmos	1.2%	
Deafness*		20.2%
Nose		
Septum Deviation	13.8%	
Discharge	4.2%	
Tender over sinuses	2.0%	
Teeth		
Poor condition	38.2%	
All extracted	14.2%	52.4%
Doubtful Tonsils*		16.4%
Enlargement of Thyroid		10.2%
Chest		
Asymmetry	6.2%	
Earlier Rickets	2.0%	
Lungs		
Dullness	8.4%	
Abnormal Sounds	16.6%	
Râles	12.2%	
Heart		
Enlarged	5.8%	
Murmurs	15.6%	
Abnormal Rale	9.6%	
Abdomen		
Mass	1.8%	
Tenderness	15.6%	
Hernia	4.8%	
Fluid	0.8%	
Enlarged Liver		2.6%
Palpable Kidney		1.8%
Enlarged Spleen		1.2%
Genital Abnormalities		2.4%
Adenopathy		
Cervical	18.4%	
Axillary	2.2%	
Inguinal	6.4%	
Skin Eruptions		27.8%
Varicosities		8.6%

*See report on special examination

TABLE XVI—Cont.

Spine		
Scoliosis	10.2%	
Lordosis	6.0%	
Kyphosis	3.0%	
Tenderness	5.0%	
Abnormalities of Extremities		25.4%
Neuro-Muscular		
Knee Jerks increased	11.4%	
Knee Jerks diminished	13.8%	25.2%
Other abnormal Reflexes	6.6%	
Romberg positive	4.2%	
Clonus positive	2.2%	
Misc. tests positive	2.4%	
Loss of sound conduction	1.6%	
Mental Abnormalities		16.0%

There is an unfortunate tendency to belittle the physical examination in these days of instruments of precision and laboratory diagnosis. Nowhere is this tendency more prevalent or fraught with greater danger than in the realm of endocrine disease. It is perfectly true that the physical findings alone seldom furnish evidence adequate for the identification of disturbed endocrine function but it is equally certain that omission of a most careful and complete physical examination has led, and will always lead, to disastrous mistakes in the interpretation of laboratory findings. Reference to the case protocols appended to this monograph will show that non-endocrine disease may simulate an endocrine disturbance in every detail but one, and that one will be found, frequently in the physical examination. This is especially true as regards diseases of the nervous system, the anaemias, tuberculosis and syphilis.

In these conditions, careful observation should elicit evidence at least strongly suggestive of organic disease, and such suggestions of endocrine disorder as are encountered should be disregarded until the examination is complete. The presence of thyroid enlargement, for example, is no indication of disturbed thyroid function, and if such significance be attributed to it, the examiner may easily overlook incipient tuberculosis, adenopathy suggestive of syphilis or leukaemia or may interpret parasthesias as suggestive of thyroid disturbance when they are in fact the early signs of a pernicious anaemia.

Even those findings which are ordinarily regarded as significant of endocrine disturbance must be regarded with caution, since all of them may be encountered in patients in whom, at the time of examination at least, no evidence of disturbed metabolism can be found. The fact that they may well be residua of previous endocrine disorder does not justify their acceptance as criteria of the present metabolic level.

An example of the danger of interpreting physical findings as diagnostic of present endocrine disturbance is afforded by obesity. Because many patients with thyroid or pituitary hypofunction are obese, there is a tendency to reason (?) that all obese patients are suffering from thyroid or pituitary failure, and to dose them accordingly, often with disastrous

results. That such a deduction is entirely fallacious is proven by the fact that practically a fourth of our "non-endocrine" patients were significantly overweight and that a considerable number of them had at one time or another been given thyroid, or other endocrine substance as a part of their reduction treatment. While obesity, especially if it be distributed asymetrically, may raise the question of endocrine disturbance, it certainly cannot be accorded any weightier significance.

Similarly, abnormal height can be suggestive only, and even thyroid enlargement and exophthalmos were found in patients in this series, the former in 10.2 per cent, the latter in 1.2 per cent. The incidence of tonsillar infection was significantly less in our "non-endocrine" than in our endocrine group, occurring in only 16.4 per cent of the former. Focal infection, therefore, occurring in patients complaining of symptoms suggestive of disturbed metabolism, on the basis of probability is suggestive of the presence of an associated endocrine disturbance, rather than an argument against it.

Disease in the heart and lungs was far more frequently encountered in our "non-endocrine" than in our endocrine patients. In the former, evidence of pulmonary abnormality was present in 37.2 per cent of patients while it was conspicuous by its absence in those showing significant metabolic disturbances. Cardiac disease was encountered in 31 per cent of our non-endocrine patients. The possibility of mild cardiac insufficiency as a cause for fatigability, vertigo, cold hands and feet, indeed for all the symptoms so commonly encountered in an "endocrine" history, must be constantly borne in mind.

Abdominal involvement would hardly seem to simulate endocrine disorders, yet 23 per cent of the patients in the series under consideration referred to as probably suffering from endocrine disturbance, showed evidence of definite intra-abdominal disorders, possibly overlooked and certainly discounted through over-enthusiastic attention to certain endocrine "stigmata."

It would also seem that evidences of disease of the central nervous system often fail to receive the consideration due them, as 25.2 per cent of our "non-endocrine" patients had abnormal knee jerks, 17 per cent showed other abnormal reflexes, and 22.4 per cent, irregular pupils, disturbed pupillary reflexes, nystagmus or strabismus. Once more it seems necessary to emphasize the point that the presence of any of these findings demands the abandonment of interest in endocrine function until proper examination has disclosed or eliminated disease of the central nervous system.

Apparently those conditions, especially in their early stages, are frequently confused with "functional disorders" since of the patients in this series submitted to complete neurological examination 61 per cent showed definite neurological conditions, and lumbar puncture gave "positive" results in 44 per cent of the patients upon whom it was performed.

TABLE XVII

SPECIAL EXAMINATIONS

Observation	No.	No. +	% +
Audiogram	159	145	91
Bacteriological	40	8	20
Barany	84	18	21
Biopsy	5	5	100
Cardiac	125	41	33
Cardiogram (Electro)	46	26	57
Dental	16	15	94
Endermal	28	15	54
Genito-Urinary	24	16	67
Laryngological	93	39	42
Liver Function	14	9	64
Lumbar Puncture	23	10	44
Lungs	36	15	42
Neurological	182	111	61
Orthopaedic	51	44	86
Otological	43	26	60
Pelvic	95	28	29
Psychiatric	46	43	93
Rhinological	93	35	38
Skin	25	23	92
Surgical	23	13	56

	Special Exam. (Eye)	323 Exam.
Abnormal		
Discs	43.7%	
Fundi	8.7%	
Pupils	10.2%	
Fields	43.0%	
Blind Spots	54.2%	

ROENTGENOGRAMS

Part	No.	No. +	%
Skull	247	55	22
Sinuses	59	37	63
Teeth	57	39	68
Heart	181	39	20
Lungs	207	79	38
G. I. Tract	37	22	59
Gall Bladder	6	6	100
Graham	9	6	67
Kidneys	10	6	60
Joints	53	34	64
Spine	44	15	34

The entire list of special examinations found necessary in the study of these "non-endocrine" patients are enumerated above, and it is only possible to emphasize here those which we have found most often necessary. These comprise complete neurological examination, examination of the upper respiratory passages and appendages, the many forms of radiologic study, and ophthalmological examinations, the latter affording perhaps more valuable aid than any other single examination in the diagnosis of the more obscure conditions encountered in this series.

In conclusion, it seems worth while briefly to restate what we have learned from the study of our "non-endocrine" patients.

First. We believe that endocrine and non-endocrine conditions often simulate each other so exactly that only by correlating complete clinical and laboratory study is differentiation possible.

Second. When clinical examination discloses evidence of organic disease, it must take precedence over any evidences of metabolic disturbance in determining the diagnosis.

Third. While the history and physical examination are essential to the differentiation of non-endocrine and endocrine conditions, clinical examination is often insufficient for the establishment of a correct diagnosis, and must be supplemented by such laboratory studies as may be necessary to reveal the status of metabolic efficiency.

In a succeeding paper will be published a series of protocols of non-endocrine cases simulating endocrinopathies.

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ENDOCRINE DISTURBANCES AMONG HIGH SCHOOL BOYS

1. Adiposo-Dystrophia Genitalis.

SHEPARD SHAPIRO, M. D.

During the past three years the Department of Health Education in the High School of Commerce of New York City has been conducting physical examinations of the students as a part of a health education program. As a result much has been accomplished in improving the health conditions of the pupils of this school through direct and personal education in hygiene. A summary of these activities is given in another publication (1). Many data have been collected in respect to the occurrence of various diseases among these pupils.

This paper deals with the endocrine disorders found among these high school boys. This subject is a very important one and merits more consideration than has been given to it in the past. There is notable lack of effort to discover and control such diseases early in life despite the fact that they are readily recognizable during the school ages. Moreover very little is being done by the Bureau of Child Hygiene to detect any of the defects in children in the high schools. In this city the task of making physical examinations of all school children devolves upon the Board of Health.

The treatment of endocrine disturbances later in life (with the possible exception of certain types of goiter) usually proves unsatisfactory. A program should be established to attack these diseases in their earliest detectable stages. The preliminary observations presented in this paper are published in the hope that the medical profession, educators, and those interested in child hygiene will take cognizance of this field of activity.

Material

Up to the present time 1850 pupils of the High School of Commerce have been examined. The medical examinations were conducted by a group of physicians practising medicine in New York City. Their services are voluntary and for scientific purposes.

The 1850 boys examined varied in ages between 12 and 19. Among them, 50 were found to have endocrine disturbances. The outstanding defect of these boys was adiposo-dystrophia genitalis. Of the 50 cases discovered 48 (2.6 per cent of the total number examined) showed this type of disease. The remaining two had simple (adolescent) goiters. In this paper only the cases of Fröhlich's syndrome will be discussed.

I have carefully examined the 48 subjects of Fröhlich's syndrome. These studies were made at school in collaboration with the teachers. Frequent reference was made to records obtained in class work. In a small number

of cases consent was obtained from the parents for metabolic studies. These were conducted at my office and included blood sugar and basal metabolic rate determinations.

Observations

The disease is characterized chiefly by: (1) fat dystrophy; (2) genital hypoplasia with absence or delay of secondary sex characteristics; (3) mental obtundity. All these are present in every case at sometime during the course of the disease but one or the other factor may be dominant.

The most striking feature in the present series is in the readjustment of the body incident to puberty and adolescence. During those periods the various elements of the disease tend to approximate normality. The symptoms do not all change simultaneously nor to equal degrees. In some cases I find that certain stigmata of the disease remain apparently unaltered.

The retarded mentality is the first element to emerge from the subnormal state. In my series this had already occurred in 47 of the 48 cases studied. The exception is a boy 16 years old who showed no progress in his work and is grouped with the ungraded pupils of the school. He presents also adiposity and genital hypoplasia to a striking degree. His weight is 250 pounds (113.9 kgm.). The girdle and pectoral obesity are very marked, and his voice is high pitched. The testes are descended but the genitalia are infantile. No indication of secondary sex characteristics is discernible. During the two years that I have been observing this boy he showed no sign of improvement in any of these elements of the disease including his mentality.

The remaining 47 pupils on the other hand show improved mentality. They are able to maintain satisfactory averages in their class work. Their ages however vary from 2 to 3 years older than the average in their respective classes which signifies that they had been backward in earlier childhood and remain handicapped by reason of this. One of these boys now excels the average pupil. During the past year he attained 90 per cent in mathematics and was among the leaders of his class in the other major subjects. This boy's mother stated that he had been noticeably backward in his childhood but that he has been rapidly coming to the fore during the past four years. He is now 16 years old and entering the third term of high school. But these changes are confined to his mentality only. The evidences of fat dystrophy and genital hypoplasia are still pronounced. (See figure 1.)

The fact that subjects of dystrophia adiposo-genitalis show rapid and progressive mental development between the ages of 12 to 16 deserves special emphasis. It is particularly important from a prognostic standpoint. The observations in this group of cases indicate that as a rule they are backward in earlier childhood but gradually emerge from this state so that by the time they reach high school age they are of average men-

tality. It is evident furthermore, that the view held by many observers that these subjects remain permanently retarded appears to be incorrect.

The psychic reactions of these boys to their physical conditions are of interest. Invariably I find evidences of self-consciousness about their unusual appearances. This has undoubtedly been aggravated by the frequent taunts of the other pupils following exposure in the swimming pool or in the shower rooms. As a result an inferiority complex develops in these boys. They seek to avoid attracting attention to themselves and consequently hesitate to participate in scholastic or extramural activities.

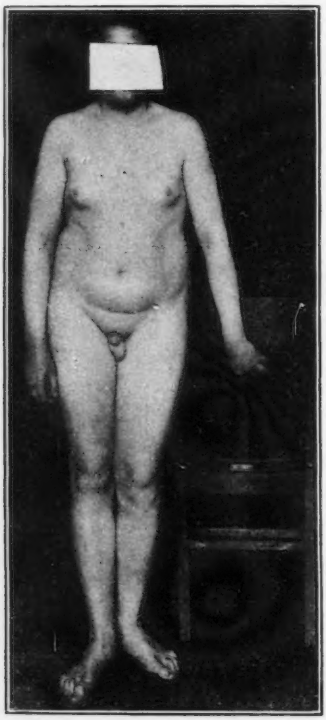

Fig. 1. Photograph of boy 16 years of age in whom the mentality has developed so that it even excels that of his classmates, but in whom the fat dystrophy and genital hypoplasia remain unchanged.

They do not mingle freely with boys of their own ages but choose as mates boys much younger than themselves. They tend to become introverts.

The hypoplastic genitalia may suddenly undergo maturation accompanied by the appearance of secondary sex characteristics. These changes occur less constantly and at a later age than the mental development discussed above but as far as I could determine may reach anatomical normality. Figure 2 is a photograph of a negro boy 19 years of age who gave a history of infantile sex development until the age of about 15

years. He now appears normal in this respect. It is interesting to note that this boy was mentally backward until his 12th year since which time he has progressed so that he is now an average student although 2 or 3 years older than the other members of his class. The fat dystrophy, girdle and pectoral obesity and large pendulous breasts are still pronounced and probably will remain permanently so.

Fig. 2. Photograph of Negro boy, 19 years of age, in whom both mentality and genitalia have developed to normal, but in whom fat dystrophy persists.

The remaining defect, fat dystrophy, seems to undergo little change. It appears from older subjects which one sees in the clinic that definite remnants of this remain throughout life.

Actually very little is known of the nature of this fat dystrophy. The opinion has repeatedly been expressed that the excessive fat deposits result from increased storage of glucose and subsequent conversion of this into fat. Supporting this is the fact that these patients usually have in-

creased tolerance for carbohydrates. In this disease also, the basal metabolism is subnormal. These phenomena are akin to those operating in thyroid deficiency.

Individuals who have dystrophia adiposo-genitalis do not as a rule eat excessively. Nor do they have ravenous appetites for sugars. In spite of this they are obese and gain weight progressively. I do not favor the idea that the adiposity is a result of subnormal heat production (basal metabolism). The low findings obtained in these cases are possibly due to altered surface area consequent to the large deposits of inactive tissue. If these cases were calculated on the basis of ideal weight many would fall within normal limits. Furthermore Shapiro and Kliatsheo (2) demonstrated that in these cases the fat dystrophy may progress even in the presence of diabetes mellitus and subnormal carbohydrate tolerance. It is obvious from these controversial findings that there remains much to be demonstrated concerning the nature and genesis of the fat dystrophy in Fröhlich's syndrome and that any explanation of it at the present time would be purely speculative. My observations in the present series of cases demonstrate further that during the period the body is undergoing the readjustment incident to puberty and adolescence the fat dystrophy lessens in degree very slightly.

Considerable difficulty is encountered in attempting to treat these high school boys. Permission was sought from the school authorities and from the parents to treat some of these pupils by organotherapy. Unfortunately, however, with one exception, these parents have not been willing to cooperate with us. This part of the program is therefore deferred until a future time.

Summary and Conclusions

About 2.5 per cent of 1850 high school students are found to have endocrine disturbances.

Forty-eight out of the 50 cases discovered are diagnosed dystrophia adiposo-genitalis.

During the readjustments incident to puberty and adolescence the three predominating elements of the disease, fat dystrophy, genital hypoplasia and mental obtundity, are found to behave differently.

The mentality is the first to emerge from the subnormal state. The subject may recover entirely from this but remains permanently handicapped by virtue of his earlier retardation.

The hypoplastic genitalia may undergo rapid and progressive development eventually approximating anatomical normality. This takes place later and less constantly than the improvement in mentality.

The fat dystrophy shows only slight change.

I wish to thank Dr. E. J. McNamara, principal, and Dr. Michael Levine, of the Department of Health Education, of the High School of Commerce, for their willing cooperation in conducting this work.

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MACROSOMIA ADIPOSA CONGENITA

A NEW DYSENDOCRINE SYNDROME OF FAMILIAL OCCURRENCE

TAGE CHRISTIANSEN, Ph.D.

From the Medical Department of Odense Hospital

DENMARK

(Physician in Chief: Prof. Dr. Knúd Schroeder)

"It happens again and again that the hereditary peculiarities of the individual are revealed only by study of the progeny, nay, often only by observations on the third generation."—*W. Johannsen:* Heredity.

Very little is definitely known as to the physiological function of the adrenal cortex. We know, however, from the pathology that *lesions* in the cortical substance may considerably influence the general somatic as well as the genital development of the organism so that this will take quite a pathological course.

The theory of the cortical substance as an independent endocrine organ dates from the beginning of this century, when Linser presented his view as to the significance of the interrenal system to the normal development of the organism. A few years later the probability of this view was confirmed by Bulloch and Sequeira on basis of their pathologic-anatomical and clinical observations on a girl, who, at the age of 10 years, began to grow excessively, became very fat, and started to menstruate. In a short time her entire habitus was that of a preclimacteric woman. Autopsy revealed a tumor originating from the suprarenal cortex. None of the other endocrine organs showed any pathological condition. From the literature Bulloch and Sequeira gathered 25 similar cases, in the which cortical tumors had also been present. Thirteen of the subjects did not have any genital symptoms.

Another valuable contribution to the clinic of the suprarenal syndromes was later furnished by Guthrie and Emery, who pointed out that *excessive obesity* as a symptom in cortical tumors is just as dominant as are pathological conditions of the genitalia. On the basis of the observations by themselves and by others, these authors set up two main types of suprarenal syndromes:

1. The *obese* type and
2. The *muscular* type ("infant Hercules").

Guthrie and Emery give 10 instances of the obese type, 7 girls and 3 boys. Autopsy showed the presence of malignant cortical tumors in 6 of the girls and in 2 of the boys. In one girl all the endocrine organs were found to be normal. Autopsy was not made on one boy.

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According to Guthrie and Emery the clinical features of the obese type are as follows: The children are puffy, with fat and pendulous cheeks which are the site of telangiectases. The skin is of a darkly congested color. Striæ distensæ may appear on abdomen and femora. Panniculus adiposus is strongly developed and usually distributed equally throughout, but the arms and legs may remain normal. The extremities are cool, cyanotic, and often the site of slowly healing ulcerations. The mammæ are large and pendulous. The expression of such patients is mostly dull, melancholic, and at times suggestive of idiocy. In some instances these children are imbecile, but most often they are psychically ahead of their age.

Abnormal hairiness is met with in all instances of cortical *tumor*, either in the form of premature pubic or axillary hair growth or as a general hypertrichosis.

Abnormal development of the genitalia is not a conspicuous feature in children of this type. Such a condition, on the other hand, *is always present in the muscular type,* in which the most distinctive signs are universal athletic muscular development ("infant Hercules"), pubertas præcox, hypertrichosis, and premature ossification of the bones.

Among the cases reported, Guthrie and Emery found no instance in which the premature development was manifest before the age of 2 years; and in every child with one of the syndromes mentioned the childish facial expression had become grown-up and old-fashioned. Guthrie and Emery reach the conclusion that the presence of tumor-like conditions in the suprarenal cortex in children may give rise to two different types of precocity, namely, the obese type, which occurs in both sexes, and the muscular type, which is found in boys only. They add that premature, relatively abnormal, hirsutes is associated with practically every instance of premature development, though it is not necessarily connected with signs of sexual maturity.

The obese type is of greatest interest to our subject; and I shall illustrate the type by briefly abstracting a case as reported by Guthrie and Emery.

This patient was a boy who at the age of 3 years began to be increasingly stout. At the same time, hairs began to appear on pubes and the upper lip. When 5 years old, he resembled "a burly brewer's drawman" in miniature. His cheeks were enormous, of a reddish color from telangiectases. The shoulders, trunk and upper extremities were the site of voluminous fat accumulations. The mammæ and the abdomen were bulging with fat. The lower extremities, however, were not particularly fat, but remarkably muscular. The hair on his head was particularly thick. The eyebrows were bushy and coalescent; the lashes long and heavy. Thick brown hair covered the back and pubes. There was an incipient mustache and beard. The development of the genitalia was in keeping with the age of the child. Intellectually he was ahead of his age, and he would make "shrewd and quaint remarks which showed considerable powers of observation." He died three months later from miliary tuberculosis. Autopsy revealed a walnut-sized tumor at the upper extremity of the kidney; microscopic examination showed the tumor to be a malignant neoplasm of the suprarenal cortex. The other endocrine organs appeared normal.

Guthrie and Emery do not attempt to give any detailed explanation of the *pathogenetic* connection between the pathologic-anatomical changes in the suprarenal cortex and the precipitate somatic development of the individual. Apert, on the other hand, divides the suprarenal syndromes into two groups according to the pathogenetic conditions he assumes to be present. One group covers the symptoms that are due to a *hyperfunction* of the cortex; the other group, the exact reverse, is made up by the symptoms that are due to a *hypofunction* of the cortical substance. Either of these conditions may, according to Apert, occur in adults as well as in children; but the clinical manifestation of such a functional disturbance will vary according to the age of the individual at the onset of the lesion. These differences, however, are not differences in quality, but merely in degree. Apert discusses in particular the influence of the cortical substance on the development of *heterologous sexual characteristics,* a question that is also considered by Guthrie and Emery.

Collett, Berner, Krabbe, and others have later made some valuable contributions to elucidate the relation between the interrenal system and the development of abnormal sexual characteristics.

The cortical hyperfunction corresponding to the cortical hyperplasia (syn. *Apert's hirsutism, Gallais' syndrome génito-surrénale*) is manifested, Apert states, by the triad: excessive obesity, hypertrichosis, and functional disturbances of genitalia; whereas hypofunction due to cortical hypoplasia is disclosed by: hypotrichosis, atrophy of the fatty tissue, and deficient somatic development (*senile nanism, progeria*). The cortical hyperfunction, which is most frequent in women, may occur at any age. The earlier its manifestation, the more definite are its symptoms. The aspects of the hyperfunction are most conspicuous when it sets in as early as the first embryonic period; for it will then result in *pseudohermaphroditism* (ovaries and uterus, panniculus, vaginal atresia, and virile secondary sexual characteristics). If the hyperfunction sets in during a later, foetal period, the secondary, heterologous sexual characteristics will be less conspicuous: the ovaries and uterus are atrophic, and there appears a universal hypertrichosis. If the cortical hyperfunction begins before puberty, it results in a premature somatic development with premature puberty, adiposity and hypertrichosis. After puberty the onset of cortical hyperfunction will result in obesity, menopause and hypertrichosis. The symptoms will be least pronounced if they do not develop prior to the climacteric period, as hypertrichosis then will fail to appear; obesity, however, and genital disturbances in form of metrorrhagia are present (Apert).

Gallais designates these results of cortical hyperfunction as *le syndrome genito-surrenale.* Collett has reported such a case of premature somatic development with hypertrichosis and virilism in an 18 months old girl. She weighed more than 15 kgm. (normal weight ca. 10 kgm.) and measured 81 cm. in length (normal length ca. 78 cm.). *The connection between the suprarenal cortex and the symptoms was obvious, as the*

successful operative removal of a cortical tumor made the signs of premature development subside.

Berner has reported an analogous case in an animal that is of the greatest interest to the comparative pathology. He demonstrated the presence of a malignant tumor, originating from the suprarenal cortex, in a virile *Leghorn hen* with marked arrhenoidism.

It should be mentioned, too, that Krabbe, who has made a valuable contribution to the explanation of the connection between heterologous sexual characteristics and the interrenal system, has reported a peculiar case of external masculine pseudohermaphroditism in a child of premature birth where one testis was replaced by a tumor consisting of suprarenal cortex cells. Krabbe's theory will not be discussed in this place, as it is of no direct import to the subject in question.

Thus Gallais, Apert, Collett, Berner, and other authors lay particular stress upon the genital abnormalities in lesions of the suprarenal cortex, whereas Bulloch and Sequeira and, especially, Guthrie and Emery *emphasize that the general premature development with hirsutes and obesity is an equally distinctive phenomenon, and that the genital changes often are lacking altogether.*

All authors, however, who have discussed the pathology of the interrenal system, are agreed that abnormal endocrine function of the cortical cells—whether due to simple hyperplasia, or to hypoplasia, to *adenoma,* or to malignant tumors—may have a pathological influence on the development of the body and genitalia so that this is accelerated, retarded, or modified sexually—according to the nature of the influence.

Opinions differ as to how this takes place. It seems most likely that the symptoms develop through a lack of endocrine coordination, which may be introduced by a dysfunction of the cortical substance, but is followed by a disturbance of the endocrine balance in such a manner as to influence, too, the secretion of other hormonopoietic organs (pluriglandular dyshormonism); these are not always, however, accompanied by any essential changes in the morphology of the secondarily affected endocrine organs.

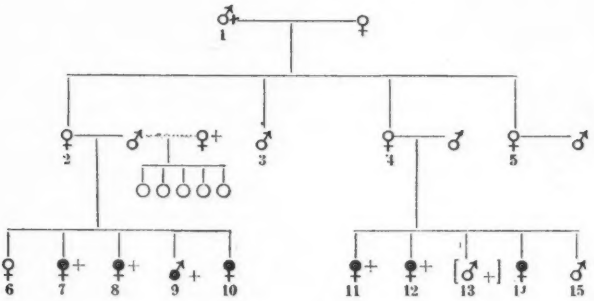
There is, however, no absolute and unexceptional dependence of the abnormal somatic conditions on the cortical lesions mentioned. For, as is well known, it is only in a relatively small number of cortical tumors that we meet with a suprarenal syndrome; and, on systematic examination of the suprarenal glands, Keilmann found cortical adenomata in a great many children of perfectly normal somatic development. The reverse condition: a typical suprarenal syndrome without demonstrable pathologic-anatomical changes in the cortical substance may likewise occur. Guthrie and Emery report such a case, in which autopsy on a 3-year-old girl of the obese type showed perfectly normal endocrine organs.

In turning to the subject, *Macrosomia adiposa congenita,* I shall first briefly outline the histories of the individual members of that family

in which I have observed this lesion (see the schema). The report is based partly on my own observations, partly on case-histories in Odense Hospital.

I have not succeeded in tracing the lineage farther back than to the grandparents of that generation in which the pathological individuals appear. But, as far as can be learned from the family members now living, *no adult* individual of this family has ever shown any sign of gigantism, stunted growth, obesity, acromegaly, or myxedema; nor idiocy, imbecility, or insanity.

SCHEMA OF THE FAMILIAL OCCURRENCE OF MACROSOMIA ADIPOSA CONGENITA



● = Macrosomia adiposa cong..

o = normal.

\+ = dead.

No. 1. Maternal grandfather, normal. Died of pneumonia at the age of 62.
No. 2. Normal woman, 32 years, with late menarche.
No. 3. Normal man, 30 years.
No. 4. Normal woman, 28 years, menstrual disturbances.
No. 5. Normal woman, 25 years.
No. 6. Normal girl, 7 years, small goiter.
No. 7. Girl with cong. macrosomia. Died 9 months old.
No. 8. Girl with cong. macrosomia. Died 4 months old.
No. 9. Boy with cong. macrosomia. Died 10 weeks old from acute glossitis.
No. 10. Girl with cong. macrosomia. *Living*, 18 months old.
No. 11. Girl with cong. macrosomia. Died 3 months old.
No. 12. Girl with cong. macrosomia. Died 6 months old.
No. 13. Boy, born 2 months before term. Died 5 days old.
No. 14. Girl with cong. macrosomia. *Living*, 4¾ years old.
No. 15. Girl, normal, 2 years.

SUBJECTS STUDIED

No. 1 on the schema is the maternal grandfather of the abnormal individuals. He died at the age of 62 years. He was normal as to somatic and mental development, and showed no sign of endocrine disturbances. Autopsy showed acute pneumonia and chronic pulmonary tuberculosis.

His widow, the maternal grandmother of the pathological individuals, is still living. She is perfectly normal. Neither of these two grandparents has any hereditary defect, as far as is known. They were *not kindred*.

Their children, who form the next generation, are all living. They are one son and three daughters.

No. 2. The oldest one of these is a 32-year-old woman of middle size and normal appearance. Physical examination reveals no signs of endocrine disturbances, but she states that *her menses did not come on before she was 20 years.* The menses have always been regular and of normal type.

She married a healthy man, in whose family there has been no abnormality of any kind, and with whom she is *not kindred,* as far as they know. By this marriage she has been mother to 5 children (Nos. 6, 7, 8, 9, 10), *of whom no less than 4 are abnormal, suffering from macrosomia adiposa congenita. Only one of her children, No. 6, the oldest, is of normal development.*

By a previous marriage the father has 5 normal children. This is a point of interest with respect to heredity.

No. 3 is a 30-year-old, single, farmer, of average height and size, and without any peculiarity.

No. 4 is a 28-year-old woman, also of normal physique and normal mentality. Like her sister (No. 2), she has married a normal and *non-kindred* man, and she has been mother to several abnormal children *(3 out of her 4 children born at full term were suffering from congenital macrosomia),* and, besides, she too gave a history of menstrual disorders. Her menses began when she was 16 years old; they have always been of very short duration (2 days), very scanty and most irregular, with intervals as long as 6 months.

No. 5 is a 25-year-old woman, perfectly normal in every respect, including the menses. She is married but has no children.

The succeeding generation comprises the abnormal children. As mentioned, this generation consists of two collateral branches: the children of the two above-mentioned sisters (Nos. 2 and 4). Here the morbidity is exceedingly high. *Among 9 children born at full term 7 were suffering from congenital macrosomia,* and only two of these are still alive (see the schema).

To make the aspects of congenital macrosomia as complete as possible, I shall now mention each of these children individually.

No. 6 is a 7-year-old girl. The pregnancy and delivery were normal. She was breast fed. The somatic development was normal. She is bright and lively. On physical examination I found a very small goiter, but no signs of hypothyroidism nor hyperthyroidism. Nor did I find any sign of other endocrine disturbances.

No. 7 is also a girl who was born at full term, by natural delivery after a normal pregnancy. She was already large at birth, but of normal proportions. She, too, was breast fed. Shortly after birth she began to grow enormously, as her length as well as her weight kept on increasing quite disproportionately; and at the age of 9 months she was "as large as a 4 years old child." Her appetite was ravenous. The urine output was excessive. She was very fat. One morning, when she was 9 months old, she was found dead in her bed, without having shown any sign of illness the preceding evening. The mother thinks that she was somewhat retarded mentally. There was no sign of premature puberty or abnormal hairiness.

No. 8 was likewise born at full term and by natural delivery. She was a large child, even at birth. Shortly after birth she began to grow excessively, just like her preceding sister (of whom she was a true copy). She, too, showed an enormous general accumulation of fat. She died at the age of 4 months, likewise unexpectedly. The genitalia were of normal development. Her mentality was normal.

No. 9 is a boy, born at full term, after normal pregnancy and by natural delivery. Like his sisters, he was large at birth and began at once to grow "beyond all measures." He died in Odense Hospital, of acute glossitis, when he was 10 weeks old. The *case-record* states that the somatic development of the child had been exceedingly rapid. He was fed at the breast, which he emptied with great avidity. He wet his diapers often and sweat considerably. His organic functions were normal. Mentally, he was ahead of his age. He could lift his head. He smiled and recognized familiar surroundings. One morning the mother noticed that his tongue rather suddenly became markedly swollen and that this swelling impeded the respiration to a large extent. The child was immediately admitted to the surgical department. On admission he weighed

6 kgm. (normal weight for his age ca. 4.5 kgm.) and measured 62 cm. in length (normal length ca. 55 cm.). The tongue was markedly swollen, especially at the root. He was foaming at the mouth. The swelling extended to both submaxillary regions. Auscultation of the lungs and heart indicated that these structures were normal. The thyroid was not palpable. The abdomen was normal. The testes, of hazel-nut size, had descended. There was no abnormal hairiness nor sign of premature puberty.

As the child was dyspnoeic and cyanotic, tracheatomy was performed at once and artificial respiration was attempted, but the patient died shortly after admission.

Autopsy: No hypertrophy of lymphoid tissue was found anywhere. The development and weight of the thyroid gland (10 gm.) corresponded with the age of the child. The parathyroid glands could not be demonstrated. The *suprarenal glands* were of normal shape and appearance, weighing 4 gm., corresponding with the age. The cut surface appeared normal. *Microscopic examination* showed mainly normal conditions; in particular, the cells appeared normal, as did the proportional amounts of cortex and medulla. The *cortical substance contained several small adenomata.* The chromaffin tissue along the aorta was well developed.

Thymus: The size, form, consistency, color, and weight (20.5 gm.) were normal and showed no definite abnormality microscopically; many Hassal's corpuscles corresponded with age of child, and a number of *eosinophile cells* diffusely and in groups along the vessels were seen. The testes were well developed, the size of a hazel-nut. The pancreas was apparently normal. The hypophysis was obtained only as formless tissue elements. The brain was very soft; the gyri and other outlines normal. There was no evidence of tumor, particularly in the hypophysis. The heart was normal (wt. 43 gm.). The liver and spleen showed no enlargement or other abnormality. The *tongue* was enlarged and firm; microscopic examination demonstrated glossitis.

These autopsy findings will be discussed later.

No. 10 is a girl, now *living*, with congenital macrosomia. At the *age of 3 months* she was admitted to Odense Hospital. At this writing she is 18 months old. She was born at full term, by natural delivery. Her weight at birth was 4 kgm. Like her sisters and brother, she began at once to grow excessively.

Fig. 1. Female patient No. 10 at the age of three months.

Her appetite was ravenous and she voided frequently. No excessive sweating, no cramps, and no tendency to spasmophilia were noted. She is said not to have been somnolent. On admission to the hospital, when 3 months old, she was enormous for her age (see Fig. 1 and 2). Her length was 71 cm. (ca. 13-14 cm. more than normal). The proportions were normal, apart from the disproportionate general hypertrophy of the subcutaneous adipose tissue, which made the entire body surface—particularly on the femora—appear as large pillows separated by deep furrows. At that time she weighed 18 kgm. (!), that is about 14 kgm. more than normal for her age. The skin was normal throughout, espe-

cially without abnormal hair-growth. There was no sign of premature puberty. The genitalia were infantile female, with no sign of hermaphroditism. There were no tetanic or rachitic stigmata. The thyroid gland was not palpable. There were no glandular swellings. She had no teeth. She cried much; her voice was strong and piercing. Mentally she seemed ahead of her age. She would smile, pay attention and recognize. The eyes were normal. Auscultation of heart and lungs gave normal findings. The abdomen was fat and large, without sign of enlarged organs or tumors. Both fontanels were open; the anterior fontanel admitted a large finger-end, and was slightly tense.

X-ray examination: No definite abnormality of the skull and, in particular, no evidence of enlargement of the sella turcica were seen. The *bones* of the body were much further developed than normal in a child of that age. All the pelvic bones were large. Well-developed centers of ossification were present in both epiphyses of the femora and tibiæ. There was a *definite center of ossification in the patella* (!). There was no center of ossification in the head of the

Fig. 2. Same patient as Fig. 1, also at three months.

radius, but well-developed centers in the external condyle of the femur and the inferior extremity of the radius. Ossification of 3 carpal bones on both sides (among these, os triquetrum [!]) was present.

Blood examination: Smears, stained after Leishman, showed erythrocytes of normal shape, size and color affinity; no immature red cells; several myelocytes, but no myeloblasts. The *differential count* showed per hundred: 35 neutrophilic polymorphonuclear leucocytes; 8 eosinophiles; 13 myelocytes; 28 small lymphocytes; 9 large lymphocytes, and 7 transitional forms.

The urine contained no blood, pus, sugar, nor albumin.

The fasting blood sugar was 0.069 per cent.

The child was very greedy; she emptied her bottle avidly. She slept almost all the time between meals. In the sitting position she salivated a great deal; and she voided frequently.

Summary: In this series of 5 children, 4 individuals were suffering from macrosomia adiposa congenita. The oldest child of the series is normal with respect to somatic development, but has a small goiter. Only one of the pathological individuals, the youngest, is still alive (18 months old).

The other series, the children of *No. 4*, comprises also 5 individuals. This series, too, has included only one child of normal somatic development.

No. 11, a girl, was born at full term by natural delivery. She was large at birth; she began at once to grow enormously. She was breast fed. She presented exactly the same features as did the patients described above. She died unexpectedly, in 1920, at the age of 3 months, and from no demonstrable cause.

No. 12, a boy, took after his sister in every respect. He likewise died unexpectedly when 6 months old, after having grown enormously large and heavy. Neither these two nor any of the other children showed any sign of premature or heterologous development of genitalia or hirsutes.

No. 13, a boy, may be left out of this survey, as he was born 2 months before full term, and died when 5 days old. For the sake of completeness, it may be added that in this case the pregnancy was complicated by premature separation of the abnormally implanted placenta.

Fig. 3. Female patient No. 14 at the age of eight months.

No. 14 is a girl. As shown by her photograph (Fig. 3), she also suffers from macrosomia. She was born at full term, in 1923. She was admitted to Odense Hospital at the age of 8 months. She is *still alive*. Her history differs really in no particular from that of her abnormal sisters and cousins: she was large at birth and began at once to grow excessively. Before long she was immensely fat. She nursed with great avidity every 3 hours, and over 20 minutes each time. In addition, she got milk-food from the age of 7 months. She cried much and was very restless if she did not get her food "on the dot." Her psychic development corresponded with her age. *Dentition began at the age of 4 months.*

On admission to hospital, the child was enormously large and fat. Her length (8 months old) was 76 cm. or 10-11 cm. more than normal; the weight was 20 kgm., or about the weight of a normal 6-year-old child. As seen from her picture, her body-surface is made up of large pillows of fat separated by

deep furrows. There is no abnormal hairiness, no abnormal development of genitalia. Sweating and turgor of the skin were normal. She had a strong voice. The posterior fontanel was closed; the anterior fontanel admitted one finger. There was no sign of acromegaly, no goiter, no rachitic, or spasmophilic stigmata. Now she had 8 teeth. Auscultation of the heart and lungs gave normal findings. There was no enlargement of the abdominal organs and no tumor. Rectal exploration showed no abnormality. The hemoglobin was 77 per cent (Sahli). The urine was normal.

As mentioned. the child is still alive (Nov. 15, 1928). I examined her in June, 1927, when she was 3½ years old.

At that time she was still very large and fat, although to a considerably less extent than at her stay in hospital 2 years before. Now she weighed 22.4 kgm., or ca. 7 kgm. above normal. She is said to have lost a great deal of weight during the past 6 months and her craving for food has become less ravenous. She measured 97 cm. in length (7-8 cm. more than normal). All the teeth were present. There was no goiter, rachitis, hypertrichosis, or premature puberty. Mentally she is backward; she can say but a few words, and she is uncleanly.

It looks then as if the somatic proportions and further development are tending toward normality. Yet she still shows signs of congenital macrosomia with relative increase of the subcutaneous fatty tissue, but there is no doubt that the violent growth of her earliest months has subsided. Mentally, she is a backward child.

No. 15 is a 2-year-old girl, born at full term. Her physical and mental development are said to have been normal, and she shows no symptoms of macrosomia, obesity, premature puberty, or any other result of endocrine dysfunction.

Summary: This series that is made up by the children of subject *No. 4,* comprises *4 children born at full term, and 3 of these suffer from macrosomia adiposa congenita.* In this connection, the prematurely born child, No. 13, is left out of consideration. One of the 3 abnormal individuals is still alive; she has now reached the age of 4¾ years. She is still suffering from macrosomia. Only one of these 4 children, the youngest, is of normal somatic development.

DISCUSSION

In surveying the histories given above, *we find that the symptoms of the congenital macrosomia have been identical in all the patients;* in fact, the resemblance of these patients is almost confusing. Symptomatologically, the 7 pathological individuals form a unity, and the manifestations of the abnormality are quite stereotypical, indicating a definite and uniform pathogenetic and etiological basis.

Macrosomia adiposa congenita, which occurs in both sexes, is a constitutional anomaly of growth that is manifested soon after birth by progressive, premature, universal development of the soma—in such a manner, however, that an excessive, endogenous deposition of fat produces a disproportion between the height and the weight of the body.

As to the skeleton, the excessive growth is evident from the increase in length as well as from the presence of premature centers of ossification and the premature dentition. The blood sugar percentage is normal. The urine contains no pathological substances. Relative eosinophilia has been demonstrated.

The increased diuresis may be explained by the copious intake of fluid —on account of the marked voracity of the children. As absolute measures

of the amount and the specific gravity of the urine are lacking, one cannot to a certainty exclude the possibility of a coexisting diabetes insipidus.

Another characteristic of these cases is *the low vitality* of these children and their lowered resistance to accidental injury, a fact that is met with in most dysendocrine conditions, particularly those associated with premature development (Biedl, Bell, Guthrie, Emery). Thus 5 of the 7 patients died in their first year of life.

As to the mental development, it seems as if such children may be ahead of their age, like the case reported by Guthrie and Emery and cited above. But, in case of No. 14 of this series, where known age (4¾ years) made a more exact judgment practicable, the patient was found to be intellectually backward.

The infantile aspect of these individuals persists in spite of the rapid development.

The development of genitalia presents no abnormality, especially as regards premature puberty and hermaphroditism.

Turgor of the skin, sweat secretion and hairiness are normal. Such endocrine organs as can be examined by palpation or x-rays—testes, thyroid, hypophysis—are of normal size and development.

The *pathologic-anatomical* findings are: Inflammatory changes (questionable) in the *thymus* and cortical adenomata of the *suprarenal glands.* The other endocrine organs are apparently normal.

On comparison of these symptoms with the *suprarenal syndromes* mentioned before, there is a conspicuous resemblance, clinically as well as pathologic-anatomically. Both conditions show premature somatic development and histological changes in the suprarenal cortex.

I therefore found it quite obvious to interpret the congenital macrosomia as a suprarenal syndrome that falls under the *obese type* as described by Guthrie and Emery. But the rapid development of the symptoms as early as in the first month of life and their extraordinary intensity—with particular respect to the obesity—the familial occurrence of the abnormality, the persistent infantile aspect of the patients, and—last but not least—the absence of hypertrichosis and of genital abnormalities, all these features distinguish macrosomia clinically from all cases previously reported, and to such an extent that *I have thought it justified to consider the condition a distinct and separate disorder and to give it a special name.*

In order to indicate the characteristics of the abnormality as definitely as possible, I have decided on the designation: *Macrosomia adiposa congenita.*

As for the *pathogenesis* of congenital macrosomia, it would be reasonable, according to Apert's theory, to assume that the development of the symptoms is due largely to the hypersecretion of a hypothetical growth-stimulating hormone, produced in the suprarenal cortex, a cortical hyperfunction—on the anatomical basis of the cortical adenomata.

But, even though this cortical hyperfunction is an important point for the understanding of the pathogenesis of macrosomia, it is, on the other hand, a question whether it is correct to take the suprarenal symptoms, in general, and the congenital macrosomia, in particular, as manifestations of a *monoglandular dysendocrinia.* The pathologists are more and more of the opinion, that *combined* symptoms—such as in congenital macrosomia, for instance—should be interpreted as the outcome of an underlying—primary or secondary—*combined* endocrine dysfunction, a *pluriglandular dyscrasia.* Such a view is precisely in line with the principal idea in the theory of humoral correlation, namely: an intimate chemical interaction of the individual elements in the endocrine system, whose aggregate, reciprocally balanced, function is of vital importance to the maintainence and physiological development of the body. This correlation will by itself bring it about that dysfunction—qualitative or quantitative —of a single organ affects the function of the other organs so that the ensuing syndrome will be the result of functional disturbances of *several* glands.

In the case of congenital macrosomia we may assume that the congenital (idiotypical) adenomatous changes of the suprarenal cortex constitute the underlying cause of the primary cortical hyperfunction, and that this in turn produces a pluriglandular functional disturbance of the respective glands, of which disturbance macrosomia adiposa congenita is the outer manifestation.

On account of its influence on the somatic development and ossification, the *thymus* probably plays a not inconsiderable rôle among these endocrine glands. The interaction of the suprarenal cortex and thymus is well known from the pathology (status thymico-lymphaticus), and it has been demonstrated experimentally by Marine, Manley and Bauman, and Jaffe, who have shown that suprarenalectomy in young animals is followed, not only by arrest of the physiological involution of thymus, but even by regeneration of this organ.

The thymic changes (accumulation of eosinophile cells), that are found side by side with the adenomata of the suprarenal cortex in congenital macrosomia, are of a certain interest in this connection. For their presence is hardly to be regarded as a purely incidental finding.

With respect to *etiology,* congenital macrosomia *must be considered the manifestation of a hereditary property* (cf. the family occurrence of the abnormality and its phenotypical conformity in the two series of children).

This property—macrosomia—may perhaps not be hereditary as such. But here—as always in the hereditary pathology—the matter does not hinge on this or that phenotypical aspect, but on the hereditary transmission of such factors as condition the development of this property in the zygote. To understand the hereditary conditions of this property, it is therefore essential not to lay particular stress on the clinical aspect of

macrosomia, but to consider this as the reflection of an endocrine disturbance, which again is the outcome of some underlying genotypical factors.

It may be said at once that an exact account of the hereditary conditions is limited by two elements. First, the family material comprises but three generations; and second, the status of the endocrine organs we are dealing with comes within the so-called complex properties, which are conditioned, not by one single factor, but by the correlation of several factors. As a matter of course, such properties are not to be expected to comply with the simple *Mendelian* rules of dissociation, unless one of these correlating factors is constantly so dominant that the phenotypical end-result is conditioned substantially by the presence of this factor (*Siemens*).

Still, the given facts do furnish material sufficient for a hypothesis of the hereditary process in these cases.

According to the available information, there has been no instance of congenital macrosomia in the direct ascendency within rememberable generations. Nor was this to be expected. For—like amaurotic idiocy, for instance, and congenital ichthyosis—this abnormality comes evidently within the so-called *lethal properties,* which are due to the presence of *lethal factors* (cf., 5 out of the 7 abnormal individuals died within the first year of life), and which are characterized by the very fact that carriers of the property, as a rule, die before they reach the age of reproduction. Consequently, a lethal property—in this case, macrosomia—can not have been present in any parent, grandparent, or direct ancestor of the pathological individuals; but, such a property may very well have been present in the side-branches, of which the family history is mostly defective. So, from that point of view, it is not strange that the parents and grandparents of the patients show no sign of macrosomia. It is more peculiar, on the other hand, that recessivity does apparently not occur. For one thing, the manifestation frequency makes against recessivity. In the second place, to make recessivity possible the fathers would have to be heterozygotic carriers of an allelomorphic character corresponding with the maternal one; and this is hardly probable, as the two fathers are not akin, nor either one of the same blood as his wife. *Most likely there is no transmission of a specific character from the paternal gametes in these cases.*

On the other hand, there can be no doubt whatever but that the mothers—the two sisters—share in effecting the hereditary production of the abnormality. The question is merely whether they both show any sign of characters that may conceivably have elicited the abnormal endocrine condition. And it seems to be so. As pointed out before, the sisters in question (Nos. 2 and 4) are not perfectly normal in endocrine respect, *as they both show menstrual disorders* (late menarche in one, and most irregular menses in the other); and no matter how commonplace this condition might appear, it can not be left out of consideration in this connection. For it is suggestive of a certain hereditary continuity—and

the correlation of the interrenal system and the gonads is a well-known fact. On the other hand, however, there is no indication of a regular dominance.

Apparently we are here dealing with a phenomenon that is not infrequent in human hereditary pathology, namely, the so-called *irregular dominance*—or, better, *conditional dominance*—which crops out as transformative inheritance—or *heteropheny* (*Siemens*). By this is meant that the same hereditary substrate is manifested differently in progenitor and progeny, and, further, that the particular property may be inherited through conductors, in spite of its dominant character.

The menstrual disorders of the mothers and the macrosomia of the children would then be interpreted as manifestation variations of the same basic properties and conditioned by the (non-specific) milieu, wherein the specific abnormal factors are placed through amphimixis.

The theoretical basis of the irregular dominance is this, that the effect of the specific pathological factors depends on what other—by themselves non-pathological—hereditary factors are admixed in the zygote, so that any transition may occur, from complete inhibition (inheritance through conductors) to maximal intensification of the effect of the factors in question.

The here mentioned hereditary dysendocrinia appears to imply the intensification (and anticipation) of a specific factor effect, increasing through generations and finally producing the lethal property, the macrosomia, through the admixture of such (non-pathological) *paternal* factors as let the *maternally* inherited factors crop out. So in this manifestation of heredity we are really in the border region between recessivity and dominance.

TREATMENT

As to the *therapy* of the congenital macrosomia, we have tried whether the ordinary organotherapeutics may have any influence on this condition. It is interesting that the very same two children, *No. 10* and *No. 14*, who were treated with such preparations, are the only ones out of 7 abnormal individuals that are still alive (see above). Whether this is due to the treatment, or whether it comes from the fact that the hospital care for several months has guarded these children against accidental injury is of course, an open question.

The experimental therapy has consisted in alternating administration of ovarian, thyroidin, and tetraglandular tablets, beside pituitrin injections. The therapeutic effect was estimated by systematic weighings and by observations on the food requirements of the children. The successive administration of the preparations was followed for several months by decrease in the rate of increasing weight (there was even a small, absolute loss of weight) and by a lowering of their craving for food, together with an apparent decrease of the diuresis.*

*This, too, supports the view that several glands share in effecting the development of this syndrome.

A cure of the macrosomia was not obtained, as mentioned, nor was such to be expected. But the treatment has unquestionably improved the condition of the patients, and it may probably have contributed to ward off—for a while at any rate—the sad, predestined fate of these children.

SUMMARY

A new dysendocrine syndrome is described and discussed. On account of its clinical aspect it is called *Macrosomia adiposa congenita.* It was met with in the children of two sisters with menstrual disorders. Among 9 children, born at full term, 7 were macrosomians; and 5 of these died within the first year of life. Autopsy (1 case) showed adenomata in the suprarenal cortex and accummulation of eosinophiles in the thymus.

Macrosomia adiposa congenita comes probably within the *obese type* of premature development (Guthrie and Emery), depending upon a hyperfunction of the suprarenal cortex (Apert); it is in a class by itself, however, through its lack of sexual abnormalities and hirsutes. Most likely macrosomia—as well as the suprarenal syndromes on the whole—is in fact a pluriglandular syndrome.

From another point of view, macrosomia adiposa congenita may be regarded as a lethal, hereditable abnormality, whose appearance may be explained as a phenomenon of transformative heredity or heteropheny (*Siemens*).

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TYPES OF GRAVES' DISEASE*

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A study of over 4000 cases of Graves' disease has led me to the conviction that so-called exophthalmic goiter is arbitrarily divisible into a number of types. A prompt recognition of some of the vague forms of the disease is of manifest benefit to the patient.

In order that a diagnosis of Graves' disease be valid, the following seven evidences should be present in combination: (1) increased basal metabolism (in approximately 99.5 per cent); (2) afebrile heart hurry (in 99 per cent); (3) tremor; (4) emotionalism; (5) fatigability; (6) dermographia; (7) relative immunity to cinchonism (d) (97 per cent). Exophthalmos and goiter, while usually present, are absent in so great a percentage of cases that the term exophthalmic goiter is misleading and should become obsolete.

Fig. 1. Graves' Disease—Incipient Type.

While increased basal metabolism is absent in approximately one out of 200 patients, and tachycardia does not obtain in approximately one per cent of cases, for practical purposes these are constant enough to be considered pathognomonic of Graves' disease. The ability to take relatively large doses of quinine (1) without evidences of cinchonism is likewise a factor which, though associated with a 3 per cent error, yet is a useful asset in diagnosis.

The division of a disease into types does not imply that these present clear-cut differentiation one from the other. In all affections, and more

*From the Bram Goiter Institute, Upland, Penn.

(1) Bram, I. Tolerance for quinine in exophthalmic goiter. Arch. Int. Med. 42: 53. 1928.

particularly in Graves' disease, types indicate either the customary clinical picture or a departure of the symptomatology from the usual in varying degree, frequently with the bearing of a greater burden by one bodily structure than by the remainder.

Fig. 2. Graves' Disease—Chronic Type.

Fig. 3. Graves' Disease—Type without Goiter.

ACUTE TYPE

The acute type of Graves' disease is rare. Its tragic course is brief and malignant, with very rapid loss in weight, extreme tachycardia, hypertension, distressing palpitation, and cardiac arrhythmia. Fibrillation, auricular and ventricular, is common. Fever may become hyperpyrexia, the temperature occasionally rising to 106 or even higher, associated with uncontrollable nausea, vomiting and diarrhea. Even hematemesis and melena may occur. Exophthalmos is marked, and trembling of the body may be so

severe as to cause vibration of the bed upon which the patient lies. The basal metabolic rate varies anywhere between plus 75 and plus 110 per cent or more. Often metabolic studies cannot be performed with accuracy because of the patient's condition. Mental derangement is common, occurring as acute delirium, dementia or mania. This form of the disease usually ends fatally from exhaustion within from a few days to a few weeks.

Fig. 4. Graves' Disease—Type without Exophthalmos.

Fig. 5. Graves' Disease—Type without Exophthalmos or Goiter.

The loss in weight may occur at the rate of one to four or five pounds a day, and cases are on record in which one-half the body weight was lost within the brief period of the patient's illness.

An acute exacerbation of the usual form of Graves' disease may approach the primary acute type in severity and is the usual cause of postoperative death. During the course of thyroidectomy or immediately after, commonly as the patient comes out of the anesthetic, there occur great excitation, marked delirium, exaggerated tremor, extreme anxiety, drenching sweats, and, at times, hallucinations and mania. The pulse mounts to

180, 190 or even 200 per minute, soon becoming feeble and impalpable; there is high fever, vomiting, and incontinence of urine and feces, usually terminating in fatal collapse within a few hours or a day or two. Postoperative crises are not quite so frequently encountered since the advent of the preoperative and postoperative use of iodine.

Fig. 6. Graves' Disease—Type with Unequal Exophthalmos.

Fig. 7. Graves' Disease—Thyroid Type.
A. Patient who had been thyroidectomized about a year before in a representative clinic. The thyroid had regenerated to an extent that knew no bounds and caused pressure symptoms.
B. Case in which iodine had caused such tremendous enlargement of the thyroid as to occasion pressure symptoms.

Thought not quite as severe as the above forms of acute Graves' disease, the crisis commonly observed in the average untreated or unsuccessfully treated case yields a clinical picture replete with anxious moments. The basal metabolic and heart rate are decidedly increased, loss in weight is accentuated, mental symptoms become pronounced occasionally to the

extent of insanity, and gastrointestinal symptoms, especially nausea, vomiting, and diarrhea may become so unmanageable as to endanger life. This may continue for a period of from a few weeks to a few months, and if the patient possesses sufficient recuperative power there occurs a gradual recession of the severity of the symptoms and once more the syndrome is that of the average case.

Fig. 8. Graves' Disease—Type with Adenoma.
A. Graves' Disease of protracted duration in which there occur adenomatous infiltration within the thyroid.
B. Graves' disease superimposed as an independent entity upon a previously existing simple thyroid adenoma.

Occurring in the average form of the disease even while the patient is tangibly improving, is the acute onset of an exaggerated symptomatology resulting from the superimposition of a recent psychic trauma or shock. Such events as automobile accidents, the sudden death of a relative, a narrow escape from a conflagration, and in one instance resulting fatally, sudden separation from her husband, were exciting causes in our series. A formerly mild case becomes severe, a sane patient insane, an organically good heart may undergo serious dilatation and fibrillate badly, and a patient in whom the prognosis appeared excellent may become moribund.

INCIPIENT .FORME FRUSTE TYPE

The early or incipient or *forme fruste* type of the disease may be somewhat difficult to recognize. The eyes may present a stare with but little tangible bulging; the thyroid gland may not be tangibly goitrous; the heart rate may be normal or increased to 90 or 100 per minute; the tremor may be unrecognizable to the inexperienced eye. Changes in behavior, nervousness, restlessness and insomnia, are in the larval stage. There may be no loss in weight; because of the excessive appetite there may indeed be an increase at this time. The basal metabolic rate may be either normal or not in excess of plus 15 or plus 20 per cent, and the patient may feel and appear in good health. On questioning, he may admit the pres-

ence of some palpitation on slight exertion, some dyspnea, nervousness and undue fatigue, but there may also be a sense of unusual exhilaration. While most cases of incipient Graves' disease develop the affection in typical form, a small percentage remain mild or early cases for an indefinite period or throughout life. Many cases of so-called puberty hyperplasia belong in this group.

AVERAGE TYPE.

The average typical case of Graves' disease requires little comment, since exophthalmos, swollen thyroid, tremor and tachycardia, render diagnosis an easy task. The condition is usually the development of the early or incipient type, although the period of transition may not be great enough to be recognized during the early stage. In other words, the average case of the disease occasionally develops more or less sharply, requiring a period of a few weeks for its full development. The well-known other features such as a pulse rate exceeding 100 per minute, a basal metabolic rate exceeding plus 20 per cent, the dermographia, sweating, loss in weight, muscular weakness, emotionalism, insomnia, and frequently diarrhea, are too well known to be discussed in detail.

Fig. 9. Graves' Disease—Cardiac Type.
A. Severe Graves' disease associated with marked cardiac hypertrophy, hypertension and impending decompensation.
B. Same condition, including marked auricular fibrillation.

CHRONIC TYPE.

Chronic typical Graves' disease is a term applicable to a form of the disease easily recognized, but rarely reaching a crisis. If crisis occurs it is not perilous. The incipient form of the disease has merged into the more characteristic and easily recognizable type, but the patient does not feel sick enough to abstain from daily duties and carries on about as before. An occasional day or a week may be spent in resting, but, generally speaking, there is no period of subjective invalidism. The skin is unduly moist, but the tremor is moderate and does not interfere with work. The heart

rate may not exceed 80 to 100 per minute, and may not be disturbing unless on unusual provocation. The thyroid gland may be moderately swollen and typically hyperplastic. The eyes, too, may present all the features of the average case. The weight may or may not be markedly reduced; and while on occasion there is marked emaciation, not infrequently a formerly obese individual may still appear obese. During remissions the basal metabolic rate may be quite within normal limits, and occasionally may even present a minus reading. During the more active stage corresponding to pseudo-crisis, it may not exceed plus 15 to 20 per cent. This form of Graves' disease may continue on without sharp manifestations for ten or more years, when spontaneous recovery may occur, with or without evidences of myxedema. Occasionally, too, an added psychic trauma may change this type to one of greater severity.

Fig. 10. Graves' Disease—Cardiac Type.

A. Very severe Graves' disease with badly degenerated heart, decompensation with anasarca.

B. A similar case in one who had undergone two thyroidectomies. Duration of Graves' disease over 14 years.

C. Beginning cardiac decompensation in a case of Graves' disease of approximately 10 years' duration.

Remark: In each of these cases auricular and ventricular fibrillation was very marked.

As a result of thyroidectomy but more often of x-ray treatment, a formerly average type of Graves' disease may become milder and chronic, without crises and often with some evidences of myxedema. Among the patients of our series is that of a man whose Graves' syndrome was of 20 years' duration, the x-ray treatments having been administered 15 years before.

Again, a formerly severe or average case of Graves' disease may undergo spontaneous remission and remain as a milder, chronic case for years or throughout life, the end resulting from events incident to an acute infection, chronic myocarditis, insanity, or a crisis following a superimposed psychic trauma.

TYPE WITHOUT GOITER.

No thyroid enlargement occurred in approximately 19 per cent of this series. In other respects the syndrome did not differ from the typical. Here we must bear in mind that thyroid swelling is usually the last event in the syndrome. Occasionally we note goiterless patients whose symptoms are more severe than those of the average. Since a normally appearing thyroid area does not preclude the possibility of an intrathoracically located thyroid, the examiner must be capable of palpating the lower border of the thyroid, and when this is impossible an x-ray examination must be made. More rarely, a patient with a normally appearing thyroid may present aberrant thyroid hyperplasia situated in relation with the pharynx, tongue, trachea, ovaries, or elsewhere.

Fig. 11. Graves' Disease—Pituitary Type.
A. Case of postoperative Graves' disease, myxedema, and acromegaly, in a man who had been thyroidectomized in a representative clinic.
B. A thyroidectomized sufferer from acromegaly.
C. A case of atypical Graves' disease and acromegaly in a woman who had not been operated upon.

TYPE WITHOUT EXOPHTHALMOS.

Exophthalmos was absent in 12 per cent of cases in this series. We must recall that in patients without exophthalmos it may occur in the advanced stage of the disease. Graves' disease without exophthalmos misleads diagnosis, especially when it is a question of differentiation from toxic adenoma. While a few observers have asserted their belief that exophthalmic goiter and toxic adenoma are virtually synonymous, there are so many points of difference in the inherent makeup of the individual, the history of the case, and the syndrome itself as to render their conclusion untenable. The uncommon instance in which Graves' syndrome is superimposed upon toxic adenoma with the superaddition of exophthalmos, merely indicates the existence of two distinct unrelated diseases. The points of similarity and of difference between toxic adenoma and exophthalmic goiter are as little and as great as the similarity and difference between chickenpox and smallpox.

TYPE WITHOUT EXOPHTHALMOS AND GOITER.

Graves' disease without exophthalmos and goiter is often most confusing, for it is here that such diagnoses as effort syndrome, paroxysmal tachycardia, hysteria, neurasthenia, early tuberculosis, and various other conditions are made. Graves' disease without exophthalmos and goiter usually presents a syndrome more amenable to treatment than the typical form of the disease.

Fig. 12. Graves' Disease—Adrenal Type.

TYPE WITH UNEQUAL EXOPHTHALMOS.

A patient may present unilateral slight exophthalmos, and by the time this becomes quite marked, the other eye may begin to protrude slightly, and throughout the course of the disease one eye may bulge more than the other. Again, during the process of recovery one eye may recede to normal while the other bulges for a time after the patient is well. Occasionally a patient may present unilateral exophthalmos throughout the entire course of the disease. There is no relationship between unequal or unilateral exophthalmos and the degree of swelling of the thyroid on one side or the other, nor is there any relationship between unequal or unilateral exophthalmos and the severity, course or prognosis of the disease.

VAGOTONIC TYPE.

The vagotonic or parasympathetic type of Graves' disease is characterized by a relatively slight increase in heart rate and little or no subjective heart symptoms. Exophthalmos is slight, the pupils contracted, there is a wide palpebral fissure with a marked von Graefe sign, and the eyes are excessively moist. Excessive sweating occurs; there is intractable diarrhea and considerable bladder irritability. There is a tendency toward hyperchlorhydria and respiratory arrhythmia. The hair does not fall out

as in the case of sympatheticotonia, and there is no tangible reduction in carbohydrate tolerance.

SYMPATHETICOTONIC TYPE.

The sympatheticotonic type of Graves' disease presents marked persistent tachycardia and subjective heart symptoms. Exophthalmos is severe, pupils are dilated, the Moebius sign is present, and epinephrin mydriasis is elicited. The eyes and skin are comparatively dry. There are no diarrhea, bladder irritability, hyperchlorhydria, nor respiratory arrhythmia. The temperature is frequently elevated to within one or two degrees above normal. There is a tendency to falling out of hair and a reduction in carbohydrate tolerance.

Fig. 13. Graves' Disease—Obese Type.
These patients illustrate Graves' disease in individuals who despite a high metabolism present a weight considerably above 160 pounds.

Let it not be supposed that sympatheticotonia or vagotonia occur as distinct entities in the clinical picture. Any attempt to check up the findings in a given patient will yield many apparent inconsistencies, so that a classification of exophthalmic goiter on this basis can be made in a relative sense only. In the average case, sympatheticotonia seems to dominate over one group of complaints and vagotonia over another, without either division of the autonomic nervous system gaining complete control. It is only when one or the other part of the involuntary nervous system holds excessive sway over the clinical picture that we might designate the type of the disease accordingly.

THYROIDAL TYPE.

To say that there is a thyroidal type of Graves' disease may be regarded as an obvious statement. When, however, we take into account the view that the thyroid is not the cause of the syndrome and when we recall that in many cases the gland does not become swollen, the need for a de-

scription of a "thyroid type" of the disease is apparent. By the thyroidal type I refer to that form of the disease in which the thyroid participates to an unusual degree in the symptomatology and, as it were, runs away with the patient. This is comparable to the common clinical phenomena in which a tonsillar infection, producing secondary rheumatic endocarditis, the latter assumes the ascendancy. The cause (largely unknown) of Graves' disease having produced thyroid hyperactivity, the latter dominates the symptomatology. The thyroid is tremendously enlarged, often to the extent of producing dyspnea, dysphagia and dysphonia. Sleep occurs in fits and starts and in a given position to ease the pressure upon the neck. In this type thyroidectomy appears the only rational therapeutic procedure. Approximately 2 per cent of cases may be considered as belonging to this type.

Fig. 14. Graves' Disease—Insane Type.
A. This patient had undergone a double ligation and developed manic depressive insanity shortly thereafter.
B. A patient who had undergone subtotal thyroidectomy and who developed a major psychosis within a few months thereafter.

TYPE WITH ADENOMA.

A sufferer from adenoma (either simple or toxic), may develop Graves' disease as an incident. The development of exophthalmos, excitability, and all the other characteristics of Graves' disease in a patient who has had an adenoma of the thyroid for some years is no reason for concluding that we have before us a case of "toxic adenoma with exophthalmos." There is no more reason to believe that Graves' disease cannot occur in a sufferer from thyroid adenoma than that the rash of measles cannot occur in a sufferer from chronic eczema.

Again, an oldstanding Graves' disease with thyroid hyperplasia may rarely undergo adenomatous, cystic, or even calcareous changes. In such an event the history of the case reveals that the various nervous manifestations of Graves' disease preceded thyroid enlargement, and that the goiter became less throbbing and less symmetrical in the course of time.

PANCREATIC TYPE.

While in nearly all cases of Graves' disease there exist a degree of carbohydrate intolerance, in approximately 3 per cent the blood-sugar approaches the height observed in diabetes and in approximately one per cent diabetes actually exists as a complication. In these cases we face a problem resembling the combination of tuberculosis with diabetes mellitus, namely the fact that the one disease requires forced feeding, the other considerable starvation.

Acidosis during the course of Graves' disease is a problem requiring determination whether acidosis is due primarily to a crisis in the syndrome or to a complicating diabetes, or both.

Fig. 15. Graves' Disease—Postoperative Type.
These two illustrations represent individuals who, despite expert thyroidectomy, are nevertheless suffering with Graves' disease in severe form.

CARDIAC TYPE.

Cases in which cardiac manifestations dominate the symptomatology may be regarded as cardiac types. The heart beats violently against the chest wall, resulting in marked discomfort and even pain. In one woman of 45 the symptoms were practically identical with those of angina pectoris. The heart rate may be out of proportion with the basal metabolic rate and the other symptoms. The blood pressure is either normal or presents a varying degree of hypertension. When decompensation is impending the blood pressure is restored to the normal figure or below. During treatment the basal metabolic rate and all other symptoms of the disease may be fairly well under control, yet the heart may still be racing for a variable time.

THYMUS TYPE.

The thymus type of Graves' disease is often seen. Graves' disease is commonly associated with enlargement of the thymus. If this organ is unusually large, tachycardia and other constituents of the syndrome are

accentuated. Male patients in whom dyspnea is out of proportion to the remaining symptomatology, whose skin is more or less of the "peaches and cream" hue, whose lymphatic glands are somewhat more prominent than usual, and whose general demeanor partakes somewhat of feminine trend, can be assumed to present the thymic form of exophthalmic goiter. While x-ray examinations are of assistance in diagnosis, they are not always convincing nor conclusive.

Fig. 16. Graves' Disease—Postoperative Type.
These three patients present a combination of marked myxedema and residuae of Graves' disease following surgical attention at representative clinics.

PITUITARY TYPE.

The patient presenting suggestive evidences of acromegaly may be regarded as a sufferer from the pituitary type of Graves' disease. A leonine expression and some thickening of the fingers and toes characterize this type. Evidences of somatic pituitary involvement may be observed in unoperated as well as operated patients. In those of adolescent age augmentation in height, even to the point bordering on gigantism, is occasionally observed.

ADRENAL TYPE.

White dermographia, hypotension in which the systolic blood pressure may not exceed 90 or 100 mm., an overpowering fatigability, and large patches of pigmentation covering the face, limbs, body, and even the mucous membranes, characterize the adrenal type of Graves' disease. Rarely, if ever, do these patients develop Addison's disease.

GONADAL TYPE.

In women the gonadal type of Graves' disease expresses itself in the presence of uterine or ovarian neoplastic conditions, sterility and marked menstrual abnormalities. In the male, sexual neurasthenia, priapism, and inferiority complexes of a sexual nature in which the mentality is more or

less directed toward the sexual self characterize this type. Sexual organs and functions are overemphasized. In most such instances the etiology of the disease is traceable to the sexual structures and life of the individual.

OBESE TYPE.

Graves' disease with obesity instead of emaciation, even in the presence of a high metabolic rate, is not unusual. The present weight may represent the natural tendency toward overweight, but not to the former extent. Thus a patient may present a weight of 160 or 180 pounds which may represent a loss of 30 or more pounds from the former obesity. Also we observe cases in which the weight before the onset of the disease was, let us say, 140 pounds, and now is increased to 150 or more. The appetite being keen in Graves' disease and the gastrointestinal tract in perfect condition, a quantity of food was taken which corresponded to more than the needs of the individual, even with the excessive catabolism, and the weight became augmented. Usually the course of the disease eventually leads to tangible loss in weight.

Fig. 17. Graves' Disease with Hypertension.
A. Case of severe type of Graves' disease in a woman of 67 with systolic blood pressure of over 200 mm.
B. A similar case in a younger woman with a systolic blood pressure of approximately 190 mm.

INSANE TYPE.

There are three forms of Graves' disease with insanity: (1) Patients who possess an inherited trait of insanity, in whom from the very outset the symptoms of the disease may be predominantly psychic. The first evidence observed may be a departure from customary behavior. The patient acts queerly and converses irrelevantly. As the disease progresses, this becomes accentuated, and in course of time a clear-cut psychosis is evident. (2) Patients who, without any known hereditary tendency, suddenly develop insanity during the course of the disease. Occasionally this may be engendered by a crisis with or without a preceding psychic trauma. The

individual becomes unmanageable, and the psychosis predominates and becomes the major problem. (3) Insanity as a result of the added shock of an operation. In our series of 18 cases of insanity complicating Graves' disease, 10 occurred in previously thyroidectomized patients. The psychosis is usually of the manic-depressive type, associated with a strong tendency to self-destruction based upon an inferiority complex and self-accusatory delusions, and accompanied by visual and auditory hallucinations. Persecutory delusions may also occur.

POSTOPERATIVE TYPE.

The outstanding features of postoperative Graves' disease as compared to the average primary form are: (1) The course is usually more protracted, response to therapeusis being rather tardy. This applies more especially to the circulatory and nervous system and the exophthalmos.

Fig. 18. Graves' Disease—Juvenile Type.
A. Typical Graves' disease of severe type in child of a little over 11 years old.
B. Severe Graves' disease in a youngster of 9.

(2) Thyroid gland regeneration is apt to resist all efforts at control for a considerable time. Indeed, the regenerative process is occasionally so mushroom-like as to lead to the formation of a goiter greater in size than was the original mass. (3) The contrary may likewise be true—the operated thyroid gland presenting such reduced function as to occasion myxedema despite the fact that the original symptoms of Graves' syndrome are largely prevalent. (4) The major psychoses, more particularly manic-depressive insanity, have a greater predilection for thyroidectomized patients than those who had not been operated upon.

NORMAL PULSE TYPE.

In approximately one per cent of cases, the syndrome, though typical in all other respects (including a basal metabolic rate of over plus 15 per

cent) yet presents a normal pulse rate. This is obviously a vagotonic manifestation, though the other symptoms may not be predominantly vagotonic.

LOW METABOLIC TYPE.

The low metabolic type of the disease (in unoperated cases) occurs in approximately 0.5 per cent of cases. Despite all evidences of typical Graves' disease, the basal metabolic rate is entirely within normal limits.

Fig. 19. Graves' Disease—Senile Type.
A. Patient 64 years old.
B. Case of severe type in a woman of 74.

HYPERTENSION TYPE.

While hypotension characterizes the average case of Graves' disease, occasionally the reverse is true in which the systolic blood pressure reaches 175 or even 200 mm. These cases may be divided into three classes: (a) those in which hypertension is secondary to a preceding hypotension, the increased blood pressure being the result of circulatory hypertrophy; (b) those with arterial sclerosis in which Graves' disease occurred rather late in life; and (c) patients in whom Graves' disease is complicated with an independent malignant hypertension.

JUVENILE TYPE.

In this series of 4000 cases, 43 were under the age of 12. A few occurred in children of three or four years old. While the circulatory and nervous systems bear the brunt of the syndrome, exophthalmos and thyroid swelling are usually moderate. The heart rate is frequently so rapid as to be entirely out of proportion with the remaining symptoms. Nausea, vomiting and diarrhea are not as frequently observed as in adults. Graves' disease in the growing child approaching puberty is frequently associated with marked augmentation in height, implying unusually active pituitary participation.

SENILE TYPE.

In our series approximately 6 per cent are beyond the age of 60. We might term this form of Graves' disease as the senile type, and their characteristics are as follows: Moderate or no thyroid enlargement, moderate exophthalmos, marked tremor, a strong tendency to hypertension, and in the presence of appropriate cooperation, satisfactory prompt response to appropriate medical attention.

SUMMARY.

In the foregoing remarks, 26 varieties of Graves' disease are briefly described. These types indicate not clear-cut species of the disease, but an accentuation or prominence of a symptom or symptoms within a clinical picture presenting many features commonly observed in all cases.

The division of Graves' disease into types is therefore largely useful arbitrary device to stimulate a deeper study of the subject and an earlier recognition of the disease in the event of marked departure of the symptomatology from the average case.

A division of Graves' disease into types will also hasten the day when it will be generally realized that Graves' syndrome can mimic more affections than any other disease in the domain of medicine, and will gain approbation to the view that since Graves' disease is neither goiter nor appears to be purely a disease of the thyroid, the synonym, exophthalmic goiter, should become obsolete as misleading and a deterrent to progress.

FROEHLICH'S SYNDROME AND ROENTGEN-RAY: SOME REFLECTIONS ON A CASE OF DYSTROPHIA ADIPOSO-GENITALIS

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CLINICAL HISTORY OF THE PATIENT

S. S. is 17 years old; 1.68 M. tall and weights 87 kgm. His face as well as the rest of his body shows a marked adiposity which forms folds on the cheeks, on a level with the lower eye-lids, which makes us think of myxedema and gives the patient's face the appearance of having a permanent smile.

Pathological antecedents. The patient has very seldom been ill, but about 3 years ago he had small-pox following which he began to get fat till he reached his present state. It is important to note that S. S. had been growing rapidly until he was completely cured.

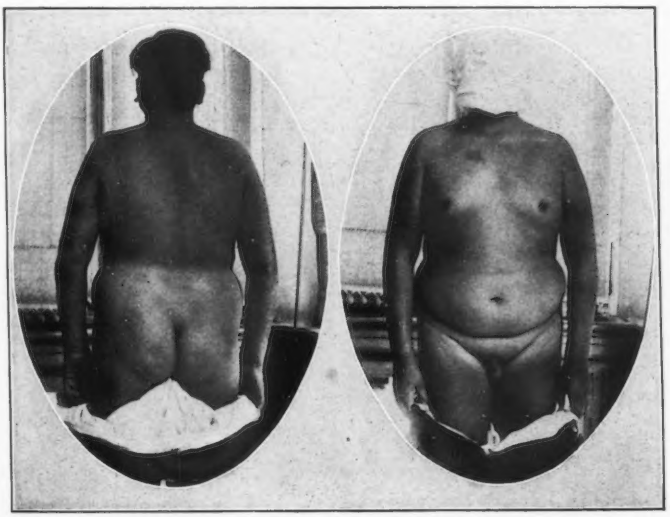

Fig. 1—View of patient's back. (November, 1926.)
Fig. 2—Front view of the same patient. (November, 1926.)

Family history. The only points worth noting are that the patient's father has nervous ties, a choreiform gait and suffers from diabetes.

Clinical examination. Naked, what most calls our attention is the marked gynandromorphism (quite feminine pectoral and abdominal outlines, great accumulations of adipose tissue on his pectorals, hips and mons veneris.) See Figs. 1 and 2.

The skin of the mons veneris forms a fold which extends on both sides of the lower abdominal region. The genital organs are rudimentary, the penis is very small and undeveloped and the right testicle almost imperceptible. (Fig. 3). The skin of this region is destitute of hair as is the rest of the body (chest and armpits). He has no sexual instinct. He has never had an erection, and has a slight genu-valgum. The Roentgenogram of the hands shows persistent epiphysial lines. (Fig. 4.) The

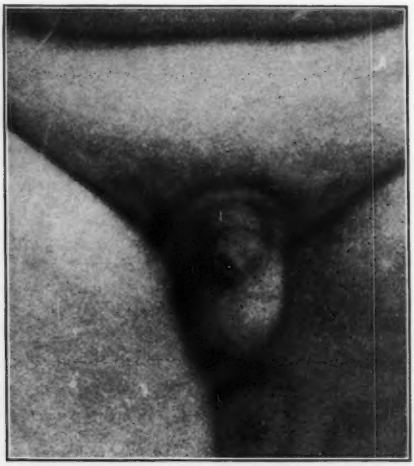

Fig. 3—Aspect of the genital organs. (November, 1926.)

Roentgenogram shows no abnormality of the sella turcica. (Fig. 5.) The patient's inclinations are towards children's games and to study. He has a good memory and great capacity for the cultivation of the sciences and above all for arithmetic. Educated in religious institutions, he seems to feel a certain propensity towards mysticism.

He has a good appetite, and does not suffer from constipation or diarrhoea.

He has no respiratory or circulatory anomalies.

His nervous system is well developed and does not show any disorder at all. He has great resistance against fatigue.

The urine does not show anything unusual in its composition and the daily quantity varies between 1500 and 2000 cc.

Pharmacodynamic tests. Goetsch's test gives a negative result. The Claude-Porak hypophysine tests (post. lobe) also give negative results: the arterial pressure (Max.=15 and Min.=8) increases one degree, but his pulse does not change. The thyroidine test of Parisot-Richard does not alter either the pulse or the pressure.

Basal Metabolism

(24th November, 1926)

Result: 1.557 Cal. per minute. 2242 Cal. in 24 hours.

Standards: Krogh, 1.387 Cal. per minute.
Boothby, 1990 Cal. in 24 hours.

Deviation: +12% (Krogh).
+13% (Boothby).

(Determinations made by Dr. Bellido. Cátedra de Terapéutica de la Fac. de Med. of Barcelona.)

Diagnosis. In effect, this is made directly and by exclusion. In both aspects we can be sure that the case of S. S. is one of a syndrome described by Fröhlich and termed by Bartels dystrophia adiposo-genitalis. That the disorder from which he is suffering may have been occasioned by malfunction of the thyroid gland is excluded by the pharmacodynamic tests and the basal metabolism. Moreover, the patient states that he has been

Fig. 4—Roentgenogram, patient's hands. (November, 1926.)

taking thyroidine for 2 years, in accordance with the prescription given by the Doctor who attended him, because his disease had been diagnosed as hypofunction of thyroid gland. Before the patient visited us for the first time, this treatment had been intensified without any useful result being obtained.

That the case is one of essential primary eunuchismus is excluded by the gynandromorphism and the proportional length of the extremities.

The origin of the hypophysial disorder which has to be considered as natural in the case in question is the small-pox, which the patient had 3 years before, because the first signs of the present syndrome appeared during his convalescence from this illness.

Where does the lesion lie? Of late years the physiology of the hypophysis has been, it may be excessively, simplified in the sense of considering it as a triple gland (anterior lobe, posterior lobe and pars intermedia). The posterior lobe has been taken to be a simple organ regulating fat metabolism or at least as regulating fat distribution in the body. From this it has been deduced that the dystrophia adiposo-genitalis must necessarily be the result of hypofunction of the posterior hypophyseal lobe. On the other hand to the anterior lobe has been ascribed control of growth and of the development of bone and the genital organs. The pars intermedia is supposed to have the same function as the posterior lobe although more intensely.

Fig. 5—Cranial roentgenogram of S. S.

If we accept this scheme as a whole we are obliged to admit in consequence that in our patient the whole of the gland has been attacked and has become hypofunctional.

Treatment. Admitting the logic of the hypothesis of the complete hypofunction, we tried to stimulate the whole function of the hypophyseal gland, choosing for preference the x-ray.

SUMMARY OF THE ROENTGEN-RAY TREATMENT

From 11th December, 1926, to 27 August, 1927, he was given 13 applications of ¼ of an Erythema dose upon the skin of different parts of the cranium (small in size in order to avoid depilation). In each application the F. S. D. was 35 cm. with port 6×8; K. V. S. 200 and 4 mA; filter 0.5 mm. Cu and 2 mm. Al.

The total radiation of the skin was 3.25 E. D., the total dosage received by the hypophysis was 1.12 E. D.

DATA OF THE SITTINGS AND PARTIAL DOSES

11th	December,	1926—	Left temporal,	(10% E. D.)
18th	"	"	" "	" "
29th	"	"	Right "	" "
8th	January,	1927—	" "	" "
14th	"	"	Anterior frontal	(7% ")
24th	"	"	Middle occipital	" "
28th	"	"	" "	" "
26th	March,	"	" frontal	" "
2nd	April,	"	Anterior "	" "
9th	"	"	Upper parietal	(10% ")
25th	June,	"	Anterior frontal	" "
9th	July,	"	Posterior occipital	" "
27th	August,	"	Right frontal	(7% ")

Fig. 6—Aspect of genital organs in August, 1927.

Results. The first results of the treatment were demonstrated after considerable delay by a marked decrease of the fat in the pectorals and in the upper zone of the hips, an increase of the diuresis (quantities above 2 litres without ever reaching 3) and the appearance of the first hairs on the genital organs. Suddenly, after 6 months' treatment (10 sittings), erections began to take place and the sexual instinct awakened. At this time the sexual organs were fairly well covered with hair, the aspect of the penis almost normal and the left testicle quite normal, while the right one had undergone marked development. (Fig. 6.) The fold of adipose tissue above the mons veneris had disappeared and the features had become much more plainly marked.

At this point of the treatment, the basal metabolism was once more determined. The following results were obtained:

Basal Metabolism

(24th July, 1927)

Result: 1.522 Cal. per minute; 2185 in 24 hours.

Standards: Krogh, 1.404 Cal. per minute.
Knipping, 2107 Cal. in 24 hours.

Deviation: + .08%

(Dr. Bellido. Cátedra de Terapéutica de la Fac. de Med. of Barcelona.)

In spite of his appearing to get thinner, the patient has gained 1 kgm. compared with his weight on beginning the treatment. It is also worth noting that during all this time he grew 2 cm. in height. The date of the last sitting was 27th August, 1927.

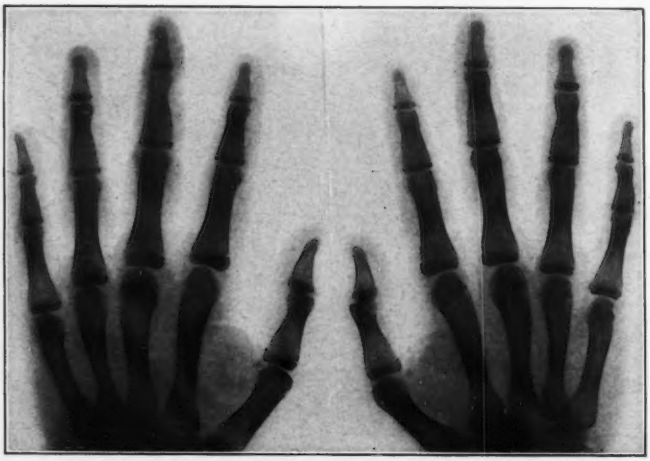

Fig. 7—Roentgenogram of patient's hands in August, 1927. The epiphysial lines still persist and it is noted that the hand has grown 1 cm. in length.

The final examination was made on the last of October and from it we deduce that S. S. is already a normal individual carrying out in a proper manner all the physiological functions, feeling all the restlessness of the normal male, and offering in the clinical examination an harmonious organic configuration. A roentgenogram shows, however, that the epiphysial lines have not yet become ossified. (Fig. 5.) This particularity has sufficient importance for us to leave it to be dealt with in another article.

The boy's father, given the results obtained, states privately that he is afraid that we may have given him too much treatment, because his fondness for study and his mysticism have disappeared and their places have been taken by a great liking for the cinema and dancing.

It is very probable that more than one case of dystrophia adiposo-genitalis, considered as a symptomatic manifestation of the classic eunuchis-

mus, has been a simple state of hypofunction or disfunction of the hypophyseal gland, or it may be a veritable Fröhlich's syndrome due to functional disorders of the hypophysis without neoplasm.

Those who may feel themselves inclined to believe that the case dealt with in this article may be one of those belonging to the category of primary eunuchismus will be able to obtain from the result of the x-ray treatment of the hypophysis ample scope for meditation.

DIABETIC COMA WITH MARKED HYPERGLYCEMIA AND RECOVERY: REPORT OF A CASE

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Relatively few cases of very marked hyperglycemia in diabetic coma, with recovery, have been published; consequently it seems worthwhile to report a case that we have had opportunity to study.

The patient, a man aged 50 years, entered the University of California Hospital on July 31, 1928, in coma. He had had symptoms of diabetes for the previous 18 months, but for the past 6 months a feeling of lassitude and weakness had been steadily increasing. His weight had decreased from 220 pounds to 195 pounds. All his teeth had been extracted just three weeks before entry with the hope of improving not only his general condition but also a neuralgic pain that had recently developed in his right arm. Instead of the anticipated improvement, however, his symptoms increased to such an extent that his vision became blurred and severe restlessness accompanied by mental depression developed. Notwithstanding these danger signals no medical advice was sought, and he finally sank into profound diabetic coma.

He entered the hospital at 1 P.M. on July 31, 1928. His face was deeply flushed, skin dry, lips a cherry red, and his breath smelled heavily of acetone. He was irrational and extremely restless. His temperature was 37° C (rectal); pulse 104 and markedly irregular due to multiple extra systoles. The respiratory rate was 32; there was but slight evidence of air hunger. Blood pressure was 130/80. Urine examination showed complete reduction of Benedict's Solution and acetone++++. *Blood sugar determination revealed the unusual hyperglycemia of 1090 mgm. per 100 cc. of blood.* The plasma was creamy white, and the blood cholesterol content was 705 mgm. per 100 cc. Unfortunately the test for plasma CO_2 was spoiled before the material reached the laboratory.

The immediate treatment, besides the giving of insulin, consisted of gastric lavage with warm water, heat to the extremities, and hypodermoclysis of 500 cc. of normal salt solution. Very soon the patient was able to take fluids by mouth, and 2500 cc. of water was given in the first 12 hours.

The urine was tested every half hour and insulin administered, the dosage varying with the degree of reduction of Benedict's solution but not exceeding 20 units per dose. From 15 to 20 units was given every

half hour so that after seven hours the patient had received 210 units. At this time the blood sugar was 601 mgm. and the blood cholesterol 670 mgm. per 100 cc. His general condition appeared to be unchanged. In the next 3½ hours, he received an additional 160 units of insulin. Thereafter for the ensuing eight hours, because the urine (tested hourly) was either entirely sugar free or nearly so, no insulin was administered. Fluids were, however, continued. At the end of this time the urine showed only a trace of sugar.

At 8 A.M., August 1, the blood sugar was 516 mgm. and the blood cholesterol 400 mgm. per 100 cc. He was now wide awake and quite alert mentally. In the first 24 hours he received 405 units of insulin and 5950 cc. of fluids consisting of 600 cc. of orange juice, 600 cc. of gingerale and 4750 cc. of water.

For the next 24 hours the urine was tested for sugar every hour from 8 A.M. until 10:30 P.M. and insulin was again administered in dosages depending upon the amount of reduction of Benedict's solution. In all, 260 units of insulin was given during this period. The patient's food consisted of 550 cc. of orange juice and 400 cc. gingerale, and the total fluid intake was 4075 cc.

On the morning of the third day the fasting blood sugar was 282 mgm. per 100 cc., and the blood cholesterol 362 mgm. A program, similar in all respects to that of the preceeding day, was maintained except that only 165 units of insulin was given. The patient received 600 cc. of orange juice and 300 cc. of gingerale, as part of a fluid intake of 3500 cc.

The fasting blood sugar on the fourth day was 154 mgm. per 100 cc. but the blood cholesterol remained somewhat high, at 345 mgm. The insulin given on this day amounted to 135 units. In addition to the fluids two soft boiled eggs were allowed.

On the fifth day he received the same amount of food—and only 75 units insulin.

A regimen was then established consisting of the following diet: CHO—100 gm., P.—40 gm., F.—10 gm. (calories—650). Insulin was given in four doses, 30 units before breakfast, 30 units before lunch, 30 units before supper and 10 units at midnight. In three days it was possible to lower the insulin by 5 units per dose. From that time on the diet was gradually increased and the insulin decreased until within two weeks after entry into the hospital, the patient was on a diet of CHO—100 gm., P.—75 gm., F.—75 gm. (calories, 1375) with 20 units of insulin before breakfast, 15 units before dinner, and 20 units before supper. His fasting blood sugar was 170 mgm. per 100 cc. and cholesterol 207.5 mgm. He remained in the hospital an additional four days, 18 days in all. On discharge from the hospital he felt well and strong and his urine was entirely sugar free. It will be noted that no alkalies were administered. It is felt that they are not only unnecessary but may at times actually produce harmful results.

A fairly extensive review of the literature reveals but two reports of individuals who recovered from diabetic coma when the initial blood sugar determinations were higher than that found in this case. Curtis (1) reported the finding of a blood sugar of 1680 mgm. per 100 cc. of blood and Foster (2) has had a patient whose blood sugar was 1260 mgm. The extreme hyperglycemia of 1740 mgm. per 100 cc. of blood reported by Argy (3) is the highest yet recorded, but his patient died. Other cases of marked increase in the blood sugar content have been reported by Pitfield (4)—1700 mgm. per 100 cc., by Joslin (5)—1370 mgm. and by Paddock (6)—1040 mgm. Their patients, however, failed to survive.

SUMMARY OF TREATMENT IN CASE RECORDED

	Blood Sugar	Insulin	Fluid
1st 24 hours	1090 mgm. per 100 cc.	405 units	5950 cc.
2nd 24 hours	516 mgm. per 100 cc.	260 units	4075 cc.
3rd 24 hours	282 mgm. per 100 cc.	165 units	3500 cc.
4th 24 hours	154 mgm. per 100 cc.	135 units	ad. lib.
5th 24 hours		75 units	ad. lib.

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ELECTROCARDIOGRAPHIC SIGNS ASSOCIATED WITH LOW BASAL METABOLISM

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In recent years the endocrine glands and conditions due to their malfunction have been subjected to intensive study. Much has been written that is obviously speculative in character, but gradually there is emerging considerable that is proven fact. It is the purpose of this article to review some of the pertinent literature on the clinical and electrocardiographic aspects of low basal metabolism and to report a study of the electrocardiographic findings in patients exhibiting a low rate of basal metabolism.

CLINICAL LITERATURE

No mention is made of any endocrine disturbance in a series of well-known books on cardiac subjects (1, 2, 3, 4, 5). Others (6, 7) speak of the heart in goiter, but do not mention thyroid deficiency. Osler (8) says that the heart is normal in myxedema. Romberg (9) has one paragraph on myxedema heart. Hirschfelder (10) says that while symptoms of cardiac weakness are present in myxedema, they are not prominent features and are of little importance in connection with disease of the heart. Simple hypothyroidism is not mentioned.

The medical journals during the past fifteen years report a few investigations on this subject. Hertoghe (11) of Belgium in 1914 wrote an excellent paper describing the symptoms and treatment of a score or more myxedematous patients. He says that infiltration which is brought on by thyroid insufficiency causes the muscle cell to increase in size so that contraction is delayed in onset and slow in execution. This applies to both the involuntary and the voluntary muscle. The above explanation might well account for the flabby heart action noted by others.

Hertoghe goes on to say that the nutrition and excretion of the nerve cell is hindered. The transmission of motor, sensory, and voluntary impulses is delayed by infiltration of the cell itself and its supporting connecting tissues. As far as the heart is concerned, this may cause cardiac pain with radiations like those of angina. Dyspnoea is present, more or less markedly according to the severity of the myxedema.

Zondek (12) in 1918 pointed out the absence of medical literature on the heart in myxedema, and reported observations upon four patients with this disorder. He found the heart to be bilaterally dilated, often to a high degree, with indolent action, slow rate, normal blood pressure, and electrocardiographic changes. After thyroid medication he noted that the

heart returned to about the normal size, the action became vigorous, the rate increased moderately, and the blood pressure remained unchanged. The electrocardiogram gradually reverted to normal.

The following year, Assmann (13) reported a case of myxedema in which Zondek's clinical observations were repeated. Digitalis, diuretin, and theocin were without beneficial effect, but the later administration of thyroid therapy was entirely successful. Zondek (14) contributed a second article in 1919.

Meissner (15) reported three more cases of myxedema, confirming Zondek's observation of the dilatation, which receded after the resort to thyroid medication. Unfortunately no electrocardiograms were obtained from these patients in the untreated stage. A few more reports by other observers have been published, but since they concerned chiefly the electrocardiographic findings their enumeration will be deferred until the subsequent section of this article.

Fahr (16) believes heart failure is a prominent feature of all cases of myxedema, and that a mild degree of heart failure, with very slight dilatation of the heart, is not at all infrequent in women patients past the age of 45, exhibiting slight but definite evidence of hypothyroidism. He reports four cases with dilatation in all the heart chambers which improved under thyroid medication after failure to respond to digitalis.

Christian (17) and Willius and Haines (18) do not agree with Fahr's conclusions. Christian (17), among 32 cases of myxedema, found only 10 showing any cardiac disturbance, and none of these resembled the type described by Fahr.

Willius and Haines (18), from a study of 162 cases of myxedema, conclude that there is no characteristic heart failure nor cardiovascular disease in this disorder.

Fahr, in a later paper (19), again insists that the term "myxedema heart" is justified, since in myxedema, symptoms of heart failure are often found which are nearly or completely relieved by the administration of thyroid extract. He finds it hard to understand why Willius and Haines failed to find heart failure in the large number (162) of cases they report. (One wonders if these were all true myxedema cases or hyperthyroidism without myxedema.) He cites several reports in the German literature which agree with his findings; that is, myxedema cases with symptoms of heart failure which were relieved when the basal metabolism had returned to normal under thyroid medication. Fahr reports six cases in this paper in which like results were noted. One subject, previously reported, had been studied four years. Her cardiac symptoms returned whenever the thyroid medication was suspended or reduced to the point of giving a subnormal basal metabolic rate.

Lawrence (20) has pointed out that depressed basal metabolism means a depression of functional activity of all the organs concerned in furnishing energy and nutrition to the body. This leads to enfeebled heart beat. He makes a distinction between myxedema and thyroid failure without

myxedema, there being greater depression of cardiac function in the former. He says that the patient with myxedema tires easily when subjected to exercise tests, but the heart rate does not increase as much as does that of a normal subject.

Means (21) states that in myxedema the cardiac output per systole may be reduced 50 per cent, and that the blood flow and work of the heart are similarly diminished.

Sturgis (22) reports 15 myxedematous patients, but evidently did not think the heart an important factor, as he omits any data pertaining to cardiac conditions, although he gives a detailed statement of findings.

Means, White and Krantz (23) question whether there is an abnormality sufficiently characteristic to justify the term "myxedema heart," but say that the condition of the heart in myxedema is important. An occasional myxedematous patient presents a type of cardiac flabbiness which is truly due to his low metabolic level. They point out that myxedema predisposes to arteriosclerosis. This may cause damage, just as it does in non-myxedematous patients. Too free use of thyroid extract in cases in which arteriosclerosis is present is dangerous because a rapid rise in metabolism increases the work of the heart by increased blood flow and may overwork a sclerosed heart. Also it has been observed that in cases of angina pectoris with myxedema the anginal symptoms often become more severe as the rate of the basal metabolism is raised to normal. Therefore, in such cases, it is important to keep the metabolic level below that at which anginal symptoms occur.

Read (24) discusses pulse rate in relation to basal metabolic rate, and states that the pulse rate varies directly with the basal metabolic rate. Sturgis and Whiting (25) agree with him in thinking that the pulse rate is of value in giving an idea of the basal metabolism. Higgins (26) found the pulse rate below 70 in only a few cases, and in some a definite increase above normal. He explains this by the fact that milder grades of thyroid deficiency are generally associated with other pathologic conditions which may alter the pulse rate; an accelerated pulse may therefore exist in spite of hypothyroidism.

LITERATURE ON ELECTROCARDIOGRAPHIC FINDINGS

The electrocardiograph has been used to a limited extent in studying patients with low basal metabolism, especially in cases of myxedema.

Zondek (12) apparently was the first investigator in this field. In his four cases of myxedema he found the P and T waves to be small or absent. After effective thyroid therapy these waves gradually reappeared, and if medication was pushed Zondek reported that the P and T waves may gradually assume an abnormal height. In his second contribution (14) Zondek reported that he used the reappearance of these waves as an indication for stopping the administration of thyroid therapy, and their diminution for resumption of the drug. This investigator also found the

heart and electrocardiogram to be normal in osteomalacia, the hypogonad state, infantilism, eunuchoidism and adiposogenital dystrophy.

Nobel, Rosenbluth and Samet (27) obtained the electrocardiograms of eleven children with myxedema and confirmed Zondek's findings in that the P and T waves were very small, sometimes absent. They then employed needle electrodes and took the current from the chest wall over the precordia. This procedure demonstrated the presence of normal P and T waves. These investigators, therefore, concluded that the abnormal electrocardiogram in myxedematous children is largely due to changed resistance in the skin, and thereby an expression of altered metabolism, but not of an abnormal mechanism of the heart. They explain the normal electrocardiograms in two of their patients (infants less than two years old) as due to the lessening of skin resistance in the very young.

These workers found the electrocardiogram to be normal in mongolian idiots.

Gardner (28) stated that he had examined the electrocardiograms of 275 patients with a low rate of the basal metabolism and found them normal save in myxedema. He does not, however, give a detailed analysis. It is clear from his article that he appreciates the fact that a low basal rate may be found in non-thyroid conditions. Gardner records six case histories of myxedema, but only a single electrocardiogram. In this he noted periods of marked auricular flutter, arborization block (so-called), and inversion of the T wave. These findings gradually returned to normal during a period of four years.

Thacher and White (29) report 14 cases of myxedema at the Massachusetts General Hospital. They believe that there is a distinct parallelism between the T wave of the electrocardiogram and the basal metabolic rate in hypothyroidism, the T wave being not more than 1 mm. in height in lead 2, instead of 2 mm. or more, as in the normal electrocardiogram. They found also a general decrease in potential of all deflections in all leads. They point out that low potential in all leads is found in myocardial exhaustion due to serious coronary sclerosis, a fact which appears to show that cardiac action is sluggish in myxedema. These 14 cases give an average heart rate of 68. There was no definitely abnormal axis deviation.

Thacher (30), in an earlier paper, found a low, flat, or inverted T in cretinism as well as myxedema. Mongolian idiots showed no electrocardiographic changes.

It has been shown (31) that the T wave of the electrocardiogram is modified by three factors: (1) Duration and order of excitation in the various fractions of the heart; (2) the relation of the anatomical axis to the recording electrodes; (3) the magnitude of the electrical resistance in the extra-cardiac tissues, especially that caused by polarization and capacity changes in the skin. A small or absent T wave associated with small initial complexes (QRS) found in myxedema and some other conditions may be

explained as the result of an increase in electrical resistance and capacity changes in the skin and tissues.

Willius and Haines (18), in their study of 55 cases, found electrocardiographic abnormalities which disappeared under thyroid medication. They note negative T waves in one or more of the three leads in 23 cases. An aberrant QRS was found in one case, delayed A-V conduction in one case, and one showed auricular fibrillation. Twenty-eight were normal.

Hamburger (32) and co-workers, in a study of 32 cases of thyroid disease, report changes in the T wave following iodine medication and thyroidectomy. They found that, in most instances, iodine medication resulted in diminution of the height of the T wave, while subtotal thyroidectomy was followed by even greater lowering. They concluded therefore that decrease in basal metabolic rate paralleled decrease in the height of the T wave in these cases.

White and Aub (33), on the other hand, found very limited parallelism between the basal metabolism and the amplitude of the T wave in a series of 27 cases of thyroid disease, but in hypothyroidism they found a low T wave which increased under treatment. In this paper, however, they record only 3 cases of low basal metabolism with T waves—0.25 mvt., 0.15 mvt. and 0, respectively.

Means, White and Krantz (23) found electrocardiographic changes involving the P wave, and low amplitude which disappeared after treatment. They do not state what they consider to be the height of the normal P wave. Fahr (16), reporting one patient only, finds a slightly atypical intraventricular block with low or flat T in all leads and a normal P. The QRS_3 was negative, as one would expect with right bundle branch block. The block disappeared after thyroid medication, the QRS became positive, and the T wave became first diphasic and later normal. When thyroid medication was discontinued, the changes reappeared. Fahr says that the QRS may be split and wide, but this is less common than changes in the T wave. A negative QRS_3 is found in severe cases with mild dilatation. In a later paper Fahr (19) reports that this patient, after six months of treatment with thyroid extract, reverted permanently to the split and prolonged QRS, despite a normal rate of basal metabolism.

Curshmann (34) was unable to confirm Zondek's findings in the electrocardiogram of patients with myxedema, and states he would not place the marked value on these signs as does Zondek.

Some significant experimental work has been reported by Lueg (35). He removed the thyroid gland from rabbits, dogs, sheep, and goats when young, and later found the P and T waves to be low (the so-called Zondek signs), and also a reversal of the ventricular complex. This investigator was able to change a normal electrocardiogram of either man or animal into one resembling that found in myxedema by using special electrodes (a few square millimetres of platinum). He measured the electrical capacity of the skin and found at certain levels the introduction of a con-

denser of 0.7 microfarads caused changes in the electrocardiogram. Lueg states that removal of the thyroid always causes a lessening of the value of the electrical capacity in the skin if a well-marked myxedema has appeared. He asserts that the changes in the electrocardiogram in myxedema are due to increased polarizability in the skin and believes that the electrical current lead off (*i. e.*, by the electrodes) from the body is no longer a true representative of the electrical changes in the heart.

PERSONAL STUDIES

The electrocardiographic data reported seemed of such interest and possible importance in diagnosis that we wished to investigate the subject further. The relatively small number of patients examined by most of the previous observers did not seem enough from which to draw conclusions. Therefore we have tried to assemble a large enough group of cases with low basal metabolism to show the frequency of the changes reported. Our study represents a total of 590 cases. We have compared the findings shown in the electrocardiograms of 260 cases with basal rates of from —10 per cent to —48 per cent, with those shown in the electrocardiograms of an equal number of patients whose basal metabolism was normal (between —10 per cent and +10 per cent) and 70 patients with a basal metabolism above normal (ranging from +10 per cent to +96 per cent).

Results. Our results show a low P wave (0.1 mvt. or less) in 96 of the 260 cases with low basal metabolism, as compared with 87 of the 260 cases with normal basal metabolism; a low T (0.1 mvt. or less) in 37 of the first group and in 46 of the second group; low R (less than 1.0 mvt.) is found in 50 of the first group as compared with 37 of the normal group (see Table I).

There is, therefore, no striking difference in the heights (voltage) of these three waves in the two groups, low P and low R being found slightly more often with a low basal metabolic rate, but low T more often in the normal group. A single low wave was found more often in the normal group, but 2 low waves were more frequent in the low basal group. Three low waves were found in 10 of the cases with low basal metabolism (2 being cases of real myxedema) and in only 3 of the normal group. Invert QRS in lead 3 was practically the same in both groups, being found 81 times in the normal and 83 times in the group of cases with low basal metabolism.*

The cases diagnosed as hypothyroid show a slightly higher percentage of low waves than is shown in the whole group, which includes other endocrine disturbances. Among the cases of hypothyroidism were many with mild myxedema, but only six in which the myxedematous state was an outstanding feature. When the electrocardiograms of this small group of

* Footnote.—Since we have been unable to find any statement in the literature quoted as to what constitutes a low P wave, we have classified as low all P waves not exceeding 0.1 millivolt in lead 2. Thacher and White (29) call a T low which does not exceed 0.1 millivolt in lead 2, and we have used this criterion in classifying the T wave as low.

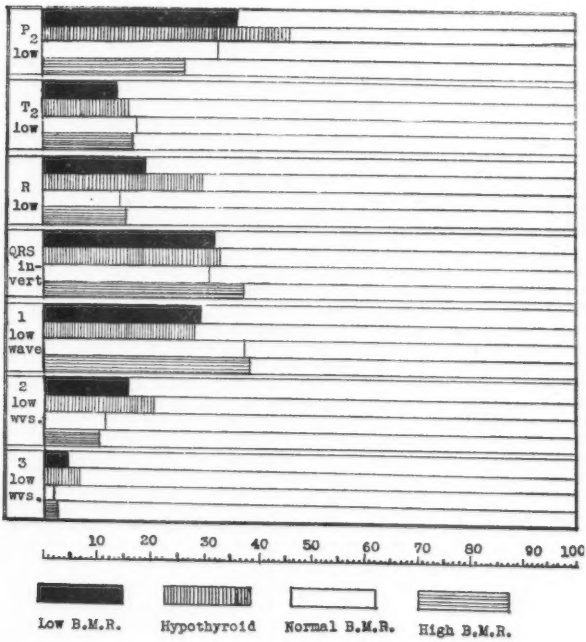
TABLE I

Comparison of the Electrocardiographic Findings in Hypothyroidism and in Low, Normal, and High Rates of Basal Metabolism

	Total Number	P_2 low %	T_2 low %	R low all leads %	QRS invert %	No sign %	No low wave %	1 wave low %	2 waves low %	3 waves low %
Hypothyroid*.....	80	41.3	16.3	30.0	32.5	32.5	45.0	28.8	20.0	6.2
Low B. M. R.....	260	34.2	14.2	19.2	31.9	39.2	52.8	29.2	15.0	3.8
Normal B. M. R.....	260	33.4	17.7	14.2	31.1	36.1	48.2	37.8	11.15	1.15
High B. M. R.....	70	27.1	17.2	15.7	34.1	37.1	51.5	38.6	10.1	1.5

*Included in low B. M. R. group.

Plate I Illustrating Table I



marked myxedemics are analyzed, five show low P and T waves, three of these having R waves less than 0.5 mvt. and two, R waves measuring 1.0 millivolt in the lead giving the maximum deflection. The sixth case had been already treated and shows normal voltage, but invert T in leads 1 and 2. None of the six have an invert QRS in lead 3.

TABLE II

Analysis of Electrocardiographic Findings in Low Basal Metabolism

Diagnosis	No. in B. M. R. Group —10% to —20%	Showing Sign Indicated		No. in B. M. R. Group —21% to —30%	Showing Sign Indicated		No. in B. M. R. Group —31% to —40%	Showing Sign Indicated		B. M. R. —10% to —40% Totals	Showing Sign Indicated	
		No.	%		No.	%		No.	%		No.	%
		P_2 1 mm. or less			P_2 1 mm. or less			P_2 1 mm. or less			Low P_2	
Hypothyroid	36	12	33.3	30	11	36.6	14	10	71.5	80	33	41.3
Pituitary	51	14	27.5	23	10	43 6	1	1	100.	76	26	34.2
Gonad	18	5	27.8	3	0	0.	0	.....	.....	21	5	23.8
Unclassified Endocr	27	5	18.5	12	2	16.6	0	.....	.....	38	7	18.4
Non-Endocrine	39	16	41.0	6	2	33.3	0	.....	.....	45	18	40.0
Total	171	53	31.1	74	25	33.8	15	11	73.3	260	89	34.2
		T 1 mm. or less			T_2 1 mm. or less			T_2 1 mm. or less			Low T_2	
Hypothyroid	36	3	8.3	30	2	6.7	14	8	57.2	80	13	16.3
Pituitary	51	5	9.8	23	2	8.7	1	0	0.	76	8	10.5
Gonad	18	1	5.6	3	0	0.	0	.....	.....	21	1	4.7
Unclassified Endocr	27	3	11.1	12	2	16.6	0	.....	.....	38	5	13.3
Non-Endocrine	39	8	20.5	6	2	33.3	0	.....	.....	45	10	22.1
Total	171	21	12.5	74	8	10.8	15	8	53.4	260	37	14.2
		All leads R less than 1 cm.			R less than 1 cm.			R less than 1 cm.			Low R	
Hypothyroid	36	11	30.6	30	6	20.0	14	7	50.0	80	24	30.0
Pituitary	51	7	13.7	23	2	8.7	1	0	0.	76	9	11.8
Gonad	18	3	16.6	3	1	33.3	0	.....	.....	21	4	19.0
Unclassified Endocr	27	3	11.1	12	2	16 6	0	.....	.....	38	5	13.3
Non-Endocrine	39	6	15.4	6	2	33 3	0	.....	.....	45	8	17.8
Total	171	30	17.5	74	13	17.5	15	7	46.6	260	50	19.2
		Negative QRS_3			Negative QRS_3			Negative QRS_3			Negative QRS_3	
Hypothyroid	36	12	33.3	30	12	40.0	14	2	14.2	80	26	32.5
Pituitary	51	18	35 3	23	4	17.4	1	0	0.	76	22	28.9
Gonad	18	5	27.8	3	1	33.3	0	.....	.....	21	6	28.8
Unclassified Endocr	27	6	22.2	12	5	41.7	0	.....	.....	38	11	29.0
Non-Endocrine	39	15	38.4	6	3	50.0	0	.....	.....	45	18	40.0
Total	171	56	32.7	74	25	33.8	15	2	13.3	260	83	31.9
		None of the above			None of the above			None of the above			None of the above	
Hypothyroid	36	12	33.3	30	13	43.4	14	1	7.1	80	26	32.5
Pituitary	51	24	47.1	23	11	47.8	1	0	0.	76	35	46.0
Gonad	18	9	50.0	3	1	33.3	0	.....	.....	21	10	47.7
Unclassified Endocr	27	14	51.7	12	4	33.3	0	.....	.....	38	18	47.7
Non-Endocrine	39	12	30.8	6	1	16.6	0	.....	.....	45	13	28.9
Total	171	71	41.5	74	30	40.5	15	1	6.7	260	102	39.2
		No low wave			No low wave			No low wave			No low wave	
Hypothyroid	36	16	44.5	30	19	63.4	14	1	7.1	80	36	45.0
Pituitary	51	33	64.8	23	12	52.3	1	0	0.	76	45	59.2
Gonad	18	11	61.2	3	2	66.6	0	.....	.....	21	13	61.9
Unclassified Endocr	27	18	66.7	12	6	50.0	0	.....	.....	38	24	63.3
Non-Endocrine	39	17	43.5	6	2	33.3	0	.....	.....	45	19	42.2
Total	171	95	55.6	74	41	55.4	15	1	6.7	260	137	52.8
		1 low wave			1 low wave			1 low wave			1 low wave	
Hypothyroid	36	15	41.7	30	3	10.0	14	5	35.7	80	23	28.8
Pituitary	51	14	27.5	23	8	34.8	1	1	100.	76	23	30.3
Gonad	18	5	27.8	3	1	33.3	0	.....	.....	21	6	28.8
Unclassified Endocr	27	5	18.5	12	4	33.3	0	.....	.....	38	9	23.6
Non-Endocrine	39	12	30.8	6	3	50.0	0	.....	.....	45	15	33.3
Total	171	51	29.9	74	19	25.7	15	6	40.0	260	76	29.2
		2 low waves			2 low waves			2 low waves			2 low waves	
Hypothyroid	36	4	11.1	30	8	26.6	14	4	28.6	80	16	20.0
Pituitary	51	3	5.9	23	3	13.0	1	0	0.	76	7	9.2
Gonad	18	2	11.1	3	0	0.	0	.....	.....	21	2	9.5
Unclassified Endocr	27	3	11.1	12	2	16.6	0	.....	.....	38	5	13.3
Non-Endocrine	39	9	23.0	6	0	0.	0	.....	.....	45	9	20.0
Total	171	22	12.8	74	13	17.5	15	4	26.6	260	39	15.0

TABLE II—Cont.

Diagnosis	No. in B. M. R Group −10% to −20%	Showing Sign Indicated		No. in B. M. R. Group −21% to −30%	Showing Sign Indicated		No. in B. M. R. Group −31% to −40%	Showing Sign Indicated		B. M. R −10% to −40% Totals	Showing Sign Indicated	
		No.	%		No.	%		No.	%		No.	%
		3 low waves			3 low waves			3 low waves			3 low waves	
Hypothyroid	36	1	2.8	30	0	0.	14	4	28.6	80	5	6.2
Pituitary	51	2	3.9	23	0	0.	1	0	0.	76	2	2.6
Gonad	18	0	0.	3	0	0.	0	.....	.....	21	0	0.
Unclassified Endocr	27	1	3.7	12	0	0.	0	.....	.....	38	1	2.6
Non-Endocrine	39	1	2.6	6	1	16.6	0	.....	.....	45	2	4.4
Total	171	5	2 9	74	1	1.3	15	4	26.6	260	10	3 8
		Pulse Av.			Pulse Av.			Pulse Av.			Pu' e Av.	
Hypothyroid	36	71.0		30	70.7		14	69.7		80	72.0	
Pituitary	53	79.0		23	74.7		1	75.0		76	77.5	
Gonad	18	78.7		3	71.6		0	.....		21	77.7	
Unclassified Endocr	27	72.7		12	75.7		0	.....		38	73.6	
Non-Endocrine	39	77.2		6	81 5		0	.....		45	79.6	
Total	171											

Plate II Illustrating Table II

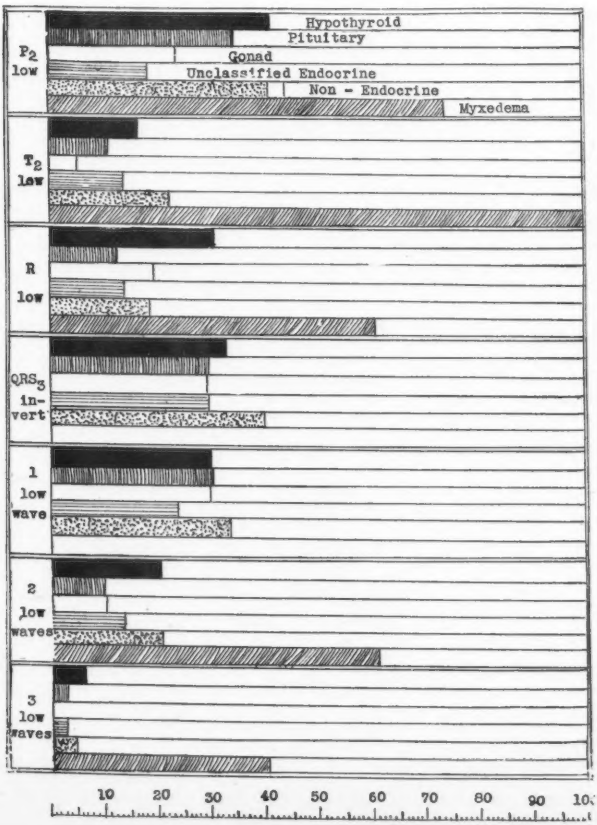


TABLE III

Analysis of Electrocardiographic Findings in High Basal Metabolism

Diagnosis	No. in B. M. R. Group +10% to +20%	Showing Sign Indicated		No. in B. M. R. Group +21% to +40%	Showing Sign Indicated		No. in B. M. R. Group +41% to +96%	Showing Sign Indicated		B. M. R. +10% to +96% Totals	Showing Sign Indicated	
		No.	%		No.	%		No.	%		No.	%
		P_2 1 mm. or less			P_2 1 mm. or less			P_2 1 mm. or less			Low P_2	
Hyperthyroid	4*	0	0.	8	2	25.0	11	3	27.3	23	5	21.7
Miscl. & Unclas. End.	12	4	33.3	3	0	0.	1	0	0.	16	4	25.0
Non-Endocrine	20	6	30.0	9	3	33.3	2	1	50.0	31	10	32.3
Total	36	10	27.8	20	5	25.0	14	4	28.6	70	19	27.1
		T_2 1 mm. or less			T_2 1 mm. or less			T_2 1 mm. or less			Low T_2	
Hyperthyroid	4*	0	0.	8	0	0.	11	0	0.	23	0	0.
Miscl. & Unclas. End.	12	1	8.3	3	1	33.0	1	0	0.	16	2	12.5
Non-Endocrine	20	4	20.0	9	6	66.0	2	0	0.	31	10	32.3
Total	36	5	13.8	20	7	35.0	14	0	0.	70	12	17.2
		R less than 1 cm.			R less than 1 cm.			R less than 1 cm.			Low R	
Hyperthyroid	4*	1	25.0	8	0	0.	11	0	0.	23	1	4.3
Miscl. & Unclas. End.	12	4	33.3	3	1	33.3	1	0	0.	16	5	31.3
Non-Endocrine	20	3	15.0	9	1	11.1	2	1	50.0	31	5	16.1
Total	36	8	22.2	20	2	10.0	14	1	7.1	70	11	15.7
		Negative QRS_2			Negative QRA_2			Negative QRS_2			Negative QRS_2	
Hyperthyroid	4*	2	50.0	8	3	37.5	11	3	27.3	23	8	24.8
Miscl. & Unclas. End.	12	4	33.3	3	3	100.0	1	0	0.	16	7	43.7
Non-Endocrine	20	5	25.0	9	3	33.3	2	1	50.0	31	9	29.1
Total	36	11	30.6	20	9	45.0	14	4	28.6	70	24	34.1
		None of the above			None of the above			None of the above			None of the above	
Hyperthyroid	4*	1	25.0	8	5	62.5	11	7	63.6	23	13	56.6
Miscl. & Unclas. End.	12	3	25.0	3	0	0.	1	1	100.0	16	4	25.0
Non-Endocrine	20	7	35.0	9	1	11.1	2	1	50 0	31	9	29.1
Total	36	11	30.6	20	6	30.0	14	9	64.3	70	26	37.1

*Of these four cases, one only was diagnosed as true hyperthyroid. One was a case of goiter with possible hyperthyroidism, in one the diagnosis was toxic thyroidosis, and in the other thyroid dysfunction.

The group with high basal metabolism shows a higher percentage of low T waves in lead 2 than does either the entire low group or the hypothyroid group, but low P in lead 2 and low R (all leads) are not found as often, though the difference is not great. A negative QRS in lead 3 is found slightly more often in the high than in either of the low groups.

These comparisons will be made clearer by a study of Table I. Table II shows the entire group of low basal metabolic cases analyzed according to diagnosis and rate of basal metabolism, and Table III compares the high basal metabolic group in like manner.

T Wave. Willius and Haines (18) reported a negative T wave in one or more leads in 23 of their 55 cases. The occurrence of T and S-T changes in our electrocardiograms is shown in Table IV.

PERCENTAGE T AND S-T CHANGES

These figures show that invert T and S-T changes are not found more often in the group with low basal metabolism than in either of the other

TABLE III

Analysis of Electrocardiographic Findings in High Basal Metabolism

Diagnosis	No. in B. M. R. Group +10% to +20%	Showing Sign Indicated		No. in B. M. R. Group +21% to +40%	Showing Sign Indicated		No. in B. M. R. Group +41% to +96%	Showing Sign Indicated		B. M. R. +10% to +96% Totals	Showing Sign Indicated	
		No.	%		No.	%		No.	%		No.	%
		No low wave			No low wave			No low wave			No low wave	
Hyperthyroid	4*	3	75.0	8	6	75.0	11	8	72.5	23	17	74.0
Miscl. & Unclas. End.	12	4	33.3	3	1	33.3	1	1	100.0	16	6	37.4
Non-Endocrine	20	10	50.0	9	2	22.2	2	1	50.0	31	13	41.9
Total	36	17	47.2	20	9	45.0	14	10	71.5	70	36	51.5
		1 low wave			1 low wave			1 low wave			1 low wave	
Hyperthyroid	4*	1	25.0	8	2	25.0	11	3	27.3	23	6	26.1
Miscl. & Unclas. End.	12	7	58.3	3	2	66.6	1	0	0.	16	9	56.0
Non-Endocrine	20	7	35.0	9	5	55.5	2	0	0.	31	12	38.8
Total	36	15	41.7	20	9	45.0	14	3	21.4	70	27	38.6
		2 low waves			2 low waves			2 low waves			2 low waves	
Hyperthyroid	4*	0	0.	8	0	0.	11	0	0.	23	0	0.
Miscl. & Unclas. End.	12	2	16.6	3	0	0.	1	0	0.	16	2	12.5
Non-Endocrine	20	3	15.0	9	1	11.1	2	1	50.	31	5	16.1
Total	36	5	13.8	20	1	5.0	14	1	7.1	70	7	10.1
		3 low waves			3 low waves			3 low waves			3 low waves	
Hyperthyroid	4*	0	0.	8	0	0.	11	0	0.	23	0	0.
Miscl. & Unclas. End.	12	0	0.	3	0	0.	1	0	0.	16	0	0.
Non-Endocrine	20	0	0.	9	0	0.	2	0	0.	31	1	3.2
Total	36	0	0.	20	0	0.	14	0	0.	70	1	1.5
		Pulse Av.			Pulse Av.			Pulse Av.			Pulse Av.	
Hyperthyroid	4*	107		8	109		11	114		23	111	
Miscl. & Unclas. End.	12	87		3	110		1	160		16	95.9	
Non-Endocrine	20	89		9	83		2	133		31	90.0	
Total	36											

*Of these four cases, one only was diagnosed as true hyperthyroid. One was a case of goiter with possible hyperthyroidism, in one the diagnosis was toxic thyroidosis, and in the other thyroid dysfunction.

TABLE IV

Percentage T and S-T Changes

Group	No change	T_2 only	T_1	—T 2 leads	—T 3 leads	S—T change
Normal	48.2	35.0	2.7	5.0	0.38	7.7
Low	55.7	36.5	0.77	2.3	0.38	6.1
High	60.0	24.3	2.86	5.7	2.86	7.1

groups. These changes, except for invert T in lead 3 (often not considered abnormal) were infrequent in any group.

Rhythm. As to rhythm, of the 260 low basal metabolic cases, 220 showed normal rhythm or sinus arrhythmia, 15 simple tachycardia and 15 normal rhythm with premature beats. Only 10 showed any significant arrhythmia, 8 being partial auriculo-ventricular block (P-R greater than 0.21 second) and 2 intraventricular block. Ninety-three had pulse rates not exceeding 70 per minute.

Of the 260 subjects with normal basal metabolic rates, 210 showed normal conditions or sinus arrhythmia, 29 simple tachycardia, 9 normal with premature beats, and 12 arrhythmia, of which 7 were partial auriculo-ventricular block, 3 intraventricular block, and 2 auricular fibrillation.

Fifty-two had pulse rates not exceeding 70.

It is evident that delayed conduction, either auriculo-ventricular or intraventricular, does not parallel low basal metabolism, since its occurrence is practically the same in both the above groups.

The rhythms found among the 70 cases of high basal metabolism were as follows: Thirty-four normal or sinus arrhythmia, 27 simple tachycardia, 4 simple tachycardia with premature beats, 2 normal with premature beats, 1 paroxysmal tachycardia, and 2 auricular fibrillation. Five had pulse rates not exceeding 70. It will be noted that conduction defects were not present in this group.

It has been stated that the electrocardiogram reverts to normal as the low basal rate rises to normal during thyroid therapy.

A second tracing was obtained in 14 cases after treatment with thyroid extract. Four showed no change in basal rate and no change in the voltage of the electrocardiographic waves. Three, which had a basal rate from 11 to 20 per cent higher in the second test, showed no change in the electrocardiogram. One subject of myxedema, whose basal metabolic rate went from —39 to —3, showed marked increase in voltage. A pituitary dysfunction case showed marked increase in basal rate with slight increase in voltage.* In one case the basal metabolic rate dropped from —22 per cent to —33 per cent, but there was no change in the electrocardiogram. Another subject whose basal rate dropped from —7 to —20 had lower voltage in the second electrocardiogram. Two others, in spite of a slightly higher basal rate showed slightly lower waves. One with an increase in basal rate of only 2 per cent showed slight increase in voltage.

In brief, then, in the 5 cases in which the basal rate was definitely higher (at least 11 per cent) at the time of the second electrocardiogram, in only 2 was the voltage higher, while in the three others it remained unchanged.

COMMENT

One of the articles on the electrocardiogram in myxedema which first came to our attention states: ". . . There is a distinct parallelism between the T wave of the electrocardiogram and the basal metabolic rate in hypothyroidism" (29). This did not agree with our experience and our contact with endocrine patients, the study of whom is the chief work of this institution (The Evans Memorial), made us aware of the difference between

* Footnote.—This was an artificial stimulation by the administration of thyroid extract. The electrical resistance at the time of the second electrocardiogram was found to be double that recorded at the first. This may have affected the voltage. It is emphasized that in comparing the voltage in different electrocardiograms, care should be taken to record the electrical resistance present when each tracing is taken. As pointed out by Katz, to whom we have referred above, the magnitude of the electrical resistance is a significant factor in the voltage of the T and other waves. It is part of our routine technic to record the electrical resistance and to photograph the standardization in each electrocardiogram.

hypothyroidism with myxedema and without the latter. Many of the reports quoted in the literature we have reviewed do not contain evidence of making this distinction. It seems probable that this very fact accounts for the diversity of the opinions on the heart in myxedema.

It is worthy of note that Fahr reported but six cases of myxedema, and stated that these were all that were found in a period of six years in the General and University Hospitals in Minneapolis. It is not surprising, therefore, that our group collected in the course of three years numbers but six patients. No one who has found the cardiac findings in myxedema as first described by Zondek, reports more than a small number of cases.

The author of the most recent report (36) expresses the opinion that there are probably two groups of cases of myxedema heart: those in which thyroid medication is followed by restoration to normal and those in which it is not. Perhaps the development of arteriosclerotic changes, to which myxedema predisposes, is the reason, for the permanency of the abnormal findings.

SUMMARY

It has been reported by various observers that patients having a low rate of basal metabolism show certain characteristic signs in the electrocardiogram. These signs are: A low P wave in lead 2; low R in all leads; a low T in lead 2; inverted T in one or more leads; delayed auriculo-ventricular conduction; and spread and notched QRS. An estimate of the reliability of these electrocardiographic signs was undertaken on a somewhat larger series of patients than had hitherto been reported.

A study of 260 low basal metabolic cases, 260 normal basal metabolic cases, and 70 high basal metabolic cases showed that the above changes were not frequent enough in the first group to be called characteristic of low basal metabolism. More than half these cases showed no low wave and only 3.8 per cent showed low potential in all three leads. The cases diagnosed as hypothyroid showed a slightly higher percentage of low voltage curves, but even in this group, nearly half showed no abnormally low waves. The findings in the group with normal and in the group with high basal metabolism were not conspicuously different. Invert QRS was practically the same in all four groups. Delayed conduction, either auriculo-ventricular or intraventricular, was found only infrequently. Invert T and S-T changes were not more frequent in the group with low basal metabolism than in the groups with normal or high basal metabolism. In the five untreated cases of myxedema, all showed low T waves, and four showed low P waves as well. R waves less than 0.5 millivolt were found in three cases, and in each of the remaining two the R wave equalled 1.0 millivolt.

In conclusion, then, no electrocardiographic findings characteristic of low basal metabolism were found in this study of 590 cases. The definitely myxedematous subjects, on the other hand, showed the changes described by other investigators.

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STUDIES ON OXYTOCIN AND VASOPRESSIN: PRESSOR ACTION*†

L. W. ROWE, M.S.

The pressor action of posterior pituitary extracts was first commented on by Oliver and Schafer (1) in 1895. The tolerance caused by large, frequently repeated, intravenous doses was noted by Howell (2) in 1898. The quantitative pressor response of a deeply anesthetized dog (Chloretone preferably) to small, infrequently repeated (not oftener than every 15 to 20 minutes) doses of pituitary extract was the basis of the earlier standardization of the first commercial preparation (Pituitrin, 1909) though the method was not published by Hamilton (3) until 1912. Largely due to the use of modifications of the proposed pressor technique the results obtained by other workers were not so satisfactory and the oxytocic test proposed by Dale and Laidlaw (4) in 1912 found favor as the method of standardization. This method seemed more logical because of the clinical use of the product in obstetrics and was recommended in the U. S. P. X in spite of the admitted difficulties attendant upon its successful application and its large experimental error (20 to 25 per cent). English workers represented chiefly by Hogben, Schlapp and Macdonald (5, 6, 7, 7A) have published extensive experimental work on the pressor effects in the spinal cat but the technique is much more elaborate than that with the chloretonized dog and the accuracy is certainly no greater.

The recent separation of two active principles—a pressor and an oxytocic principle—from pituitary extract by Kamm, Aldrich, Grote, Rowe and Bugbee (8) proves the necessity for the use of a pressor method of standardization as well as the oxytocic method. For that reason some of the results of about 20 years' experience with the pressor method in this laboratory together with pressor experiments with the separated principles will be detailed in the hope that some of the difficulties encountered by others may be solved and a basis for a more universally acceptable pressor method may be reached.

THE PRESSOR TECHNIQUE

Since this was first described (3) and later defended in 1916 by Hamilton and Rowe (9) further experience over a period of twelve years has only served to strengthen our belief in the necessity of using a pressor method and in the relative accuracy and practicability of our present technique. Closely following this publication (9) further experience with the oxytocic method gave more favorable results and for fully ten years both methods have been in constant use in this laboratory.

*Contribution from the Medical Research Laboratories of Parke, Davis & Co., Detroit, Michigan.

†The names under which these active principles are now available are Pitocin and Pitressin, respectively.

Healthy dogs, preferably of medium size and short-haired, are completely anesthetized by chloretone. A 40 per cent solution of chloretone in 40 per cent alcohol is injected intraperitoneally, using about 1 cc. per kgm. body weight [for details see article on chloretone anesthesia (10)]. This gives a deep, steady, lasting anesthesia with a lowered blood pressure but one which responds quantitatively and, in most animals, to a satisfactory degree. Small doses corresponding to 0.04 cc. (1 cc. of a 1 to 25 dilution) of U. S. P. X standard pituitary extract are given intravenously not oftener than every 15 minutes and the rise in blood pressure recorded on a kymograph from one of the carotid arteries. The first reaction on any animal should usually be disregarded as it does not entirely agree with succeeding reactions from the same dose. Comparison of the quantitative pressor action produced by the doses of "standard" and "unknown" on the same animal at alternate intervals will ultimately give two sets of equivalent reactions which complete the pressor assay of the unknown. Adjustment to 100 per cent potency and a second assay complete the pressor standardization of the preparation.

PRESSOR STANDARD

The almost universal adoption of the international unit of oxytocic activity indicates the need of an analogous pressor unit. In our first publication on the separated principles (8) we suggested in a preliminary way a pressor standard such that standard pituitary extract U. S. P. X would contain 10 pressor units per cc. and standard desiccated posterior lobe U. S. P. X would contain 2 pressor units per mgm.

This subject was carefully considered at the meeting of the Health Committee of the League of Nations held at Frankfort, April 25th to 28th, 1928, and the following statement was made: "The Commission further recommends that the activity of any such preparation should be expressed in relation to the international standard in units of *pressor* or *oxytocic* activity, and that, in each case, *the unit of such activity* shall be that of 0.5 mgm. of the standard powder." The adoption of this logical pressor unit by such an international body would seem to place the final stamp of approval upon it as a means of stating definitely pituitary potency of this type.

In my experience of fifteen years with this method it has frequently happened that as many as 25 or 30 quantitative reactions have been obtained from one animal without the slightest evidence of tolerance or of depressor action. These have been the objections voiced by critics of the pressor method and, in my opinion, they are due to an insufficient depth of anesthesia as well as an insufficiently lowered blood pressure. With ether or chloroform anesthesia or even with incomplete chloretone anesthesia I have often seen the depressor effect which precedes the pressor and this detracts from the accuracy of the test. With such conditions prevailing neither the depressor nor the pressor action of a given dose can be

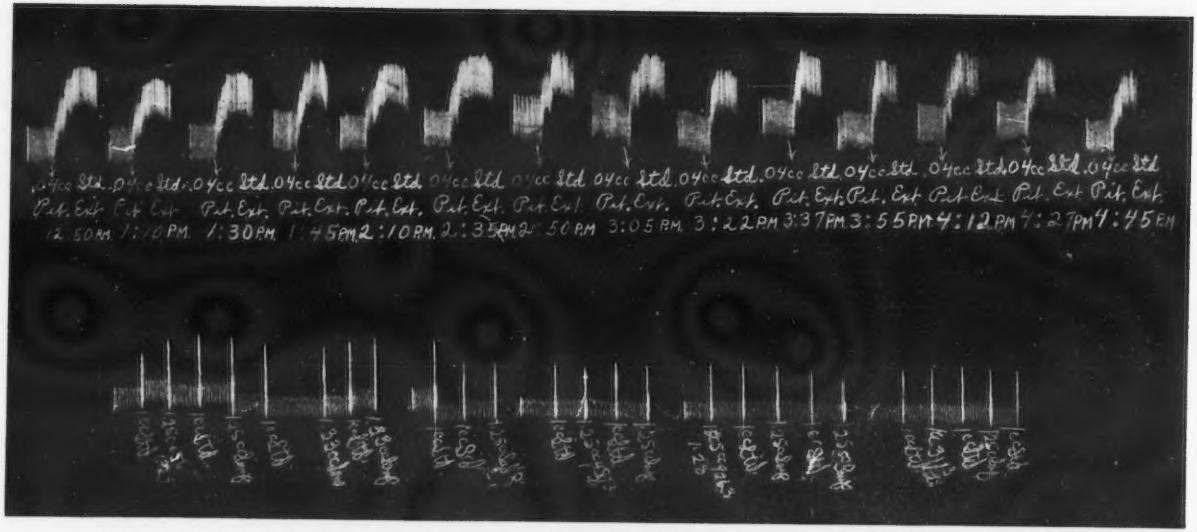
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Figure 1. Above, partial detail of 14 successive standard doses. Below, abbreviated reactions for routine pressor tests.

depended upon to be quantitative. With the proper depth of anesthesia (which can best be attained by a very large single dose of chloretone) it often happens that an accuracy of $\pm$ 10 per cent can be obtained while other animals may be used to give approximate results to be checked later. Fig. 1 shows a large number of consecutive injections into one dog without tolerance and depressor action (the first reaction is a little greater than the rest). This Fig 1 shows the contrast between partially detailed reactions and abbreviated reactions. The latter we always use for routine pressor work because of the ease of comparison and the conservation of tracing space.

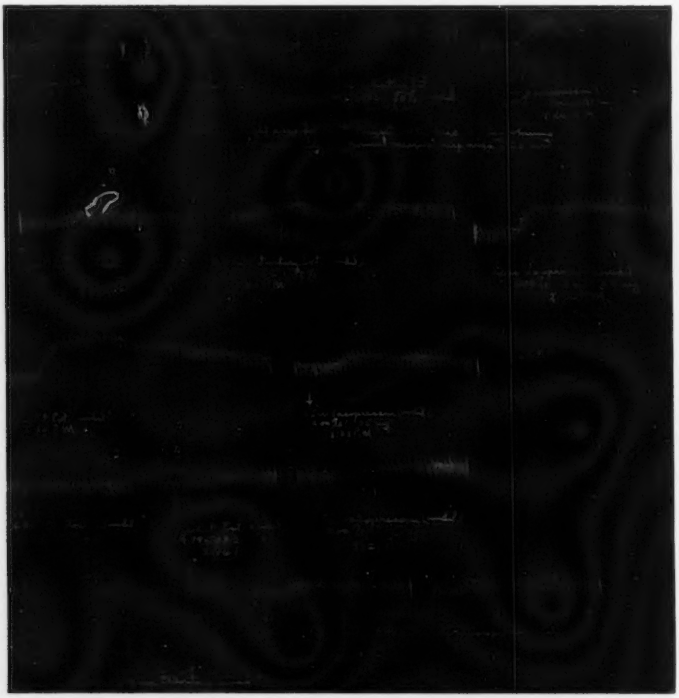

Figure 2. Effect of degree of anesthesia upon pressor action. Small and large doses. Light and deep anesthesia.

EXPERIMENTAL DATA

The pressor action of the separated fractions, Vasopressin and Oxytocin, has been the subject of considerable experimentation. In the article announcing the separation of the active principles (8) few details were given of the pressor action but the absence of histamine was mentioned. Very recently Gaddum (11) has published some work on the separated principles which also shows the absence of histamine. Fig. 2 shows the detailed effect of large and small doses of Pituitrin, Vasopressin and Oxy-

tocin under light and deep chloretone anesthesia. It will be noted that with the first four reactions the anesthesia was so light and the blood pressure so high that small doses produced only a slight pressor action and in two cases this was preceded by a slight depressor action. Later with the same animal under deep chloretone anesthesia there was no tendency to depressor action, even with large doses, though there was a marked development of tolerance due to the large doses.

This depressor action of pituitary extract under certain test conditions has been the subject of concern to many pharmacologists. Since histamine in very small amounts produces such a marked fall in the blood pressure of an anesthetized dog it was natural to assume that this depressor action might be due to histamine. Such depressor action which is frequently encountered is not characteristic of ordinary doses of fresh pituitary extracts and is not produced under conditions where histamine in very small amounts will produce a marked depressor effect.

This alone would rule out histamine as the cause of the depressor action which can be produced either by pituitary extracts or very large doses of oxytocic fraction.

Figure 3. Rather large doses of Pituitrin, Vasopressin, Oxytocin and Histamine after treatment with sodium hydroxide. Also small dose of Pituitrin before treatment.

As a further proof of the absence of histamine in these fractions potent solutions were treated with strong sodium hydroxide solution (2N.) for at least one hour with the result that both the pressor and oxytocic activities were totally destroyed (see Fig. 3). Histamine hydrochloride in a 1 to 10,000 solution when similarly treated was still active as a depressor and oxytocic agent. There is another more logical explanation of the depressor action and that is the excess acid. Ordinary pituitary extracts contain 0.25 per cent free acetic acid and Fig. 4 shows the depressor action of 2 cc. of undiluted pituitary extract compared with that caused by 2 cc. of 0.25 per cent acetic acid on a dog anesthetized with ether. Abel (12) produced a marked depressor effect on an etherized cat with a very

large dose (8.75 mgm. in 2 cc.) of his highly purified tartrate. The blood pressure was abnormally high when the second and larger dose was given and the excess acid was evidently stronger than the pressor principle.

Tolerance to Vasopressin can be developed just as to Pituitrin with improper technique. Small doses repeated too frequently will produce such a result even in an animal that is properly anesthetized. Figs. 4 and 5 show the tolerance from large and small doses of both Pituitrin and Vasopressin under chloretone and ether anesthesia and the lack of tolerance with small doses and proper anesthesia.

It will be noted from Fig. 4 that a small dose of Pituitrin and Vasopressin first produced a marked rise in blood pressure while a rather large dose of Oxytocin produced a very small pressor effect. Later when larger doses were given more frequently tolerance developed so rapidly that 100

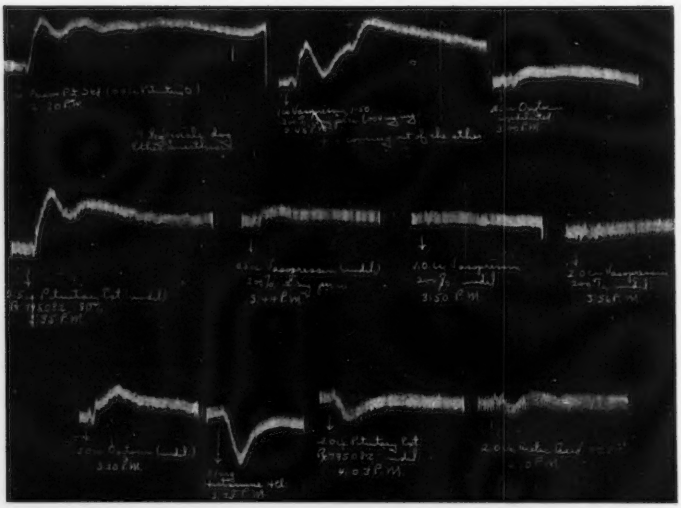

Figure 4. Pressor action with dog under ether. Tolerance from large doses. Depressor action from Pituitrin and acid.

times as much Vasopressin produced no pressor effect though it also produced no depressor effect. Histamine still produced a marked and characteristic depressor effect.

Figure 5 shows the consistency of pressor response in No. 2 to No. 7 after No. 1 was a little greater than the rest. No. 8 to No. 12 show a definite degree of tolerance from the same small doses repeated every 10 minutes instead of every 15 or 20 minutes. No. 13 shows the return to normal reaction after a 20-minute rest. No. 14 to No. 18 show a still smaller response from the same small dose given every 5 minutes. No. 19 to No. 23 show the tolerance to large doses of Vasopressin when these are given too frequently. No. 25 is the result of a large dose of Oxytocin and

shows little, if any, depressor or pressor action. No. 25 is the characteristic depressor effect from a very small dose (0.1 mgm.) of histamine.

The use of different anesthetics such as ether, chloralose, etc., has been tried and it seems apparent that not quite as great a degree of accuracy can be expected with the animal under these anesthetics as under chloretone. A deep, steady and safe anesthesia could not be maintained with these anesthetics and even when the anesthesia was fairly deep the blood pressure was not low enough to prevent an occasional depressor reaction.

SUMMARY

1. The pressor action of Vasopressin (the pressor principle of posterior pituitary extract—now Pitressin) is shown to be entirely similar to that of an active extract.

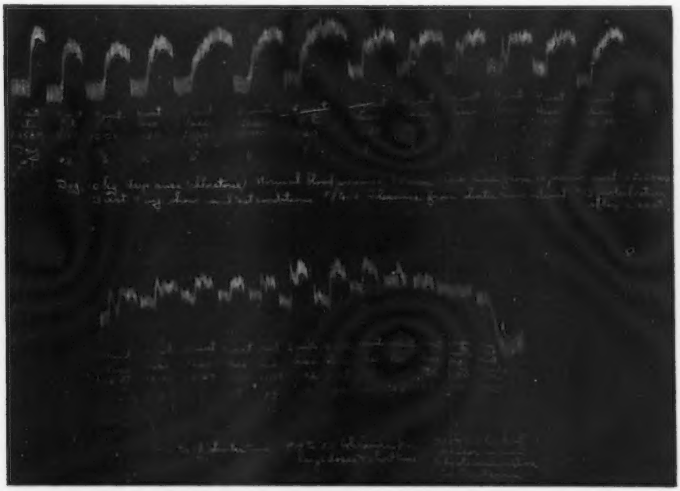

Figure 5. Lack of tolerance (1 to 7). Tolerance short time (8 to 12), large doses (19 to 23). Lack of pressor or depressor in large dose of Oxytocin.

2. The pressor action of Oxytocin (the oxytocic principle of posterior pituitary extract—now Pitocin) is shown to be chiefly due to the presence of the very small amount of unseparated vasopressin.

3. Neither vasopressin nor oxytocin produces a depressor action under proper test conditions.

4. Evidence is submitted to show the absence of an appreciable amount of histamine in either vasopressin, oxytocin or pituitrin.

5. Tolerance to vasopressin as to pituitrin can be produced with large or even small doses injected too frequently and lack of tolerance can also be shown with proper test conditions.

6. The technique of a pressor method which has proven satisfactory and practical as a quantitative index of pressor potency of pituitary extracts over a period of 20 years is again given in detail and suggested for adoption as the standard method of assay for this type of pituitary activity.

7. A pressor unit is defined which is logical and analogous to the international oxytocic unit. This pressor unit was suggested previously and was tentatively adopted at the recent Frankfort conference of the Health Committee, League of Nations.

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Book Reviews

THE SIMPLE GOITER. Robert McCarrison. William Wood & Company, New York.

Reviewed in Arch. Int. Med. 42:607-608. 1928.

HORMONE UND INNERE SEKRETION. Fritz Laquer. Theodor Steinkopff, Dresden und Leipzig. 1928. Pp. 136.

The size of this little volume gives no hint as to its extensive content and the laborious effort involved in its production. A chapter is devoted to each of the recognized endocrine glands. This includes a short historical background, the hormone and its physiological effects and the clinical picture of dysfunction. The literature, as far as the author considers it significant, is brought down to date by some twelve hundred citations. In general this includes the work done since 1922. Careful reading of this volume will give a birdseye view of the general field of endocrinology and a new appreciation of its extent. In a volume of this nature the value of the work would be increased if the titles of the papers were included in the bibliography.

ENDOKRINE KRANKHEITEN. Hans Curschmann. Theodor Steinkopff, Dresden und Leipzig. 1927. Pp. 151.

The purpose and extent of this volume is best stated by the author in his preface. A free translation follows.

This small book will not and cannot exhaust the extensive literature. For that purpose voluminous handbooks are available now. It will, however, give clinical pictures of the more common endocrine diseases based upon a relatively large number of peculiar cases which with due consideration of the theoretical gives to the practical art that which is to it the most important—pathology, symptomatology and therapy.

The author describes the more common endocrine diseases in the usual manner and illustrates a number of them with photographs of his own patients.

THE COMPARATIVE PHYSIOLOGY OF INTERNAL SECRETION. Lancelot T. Hogben. The Macmillan Company, New York; The University Press, Cambridge, England. 1927. Pp. 148.

While not nearly as concentrated or extensive as Laquer, this little volume presents the more conspicuous features of the endocrine situation

to date. The usual method of discussing the subject gland by gland is avoided. Physiological activity is used as a basis for chapter division, e. g., "Chemical Coordination," "Endocrine Factors in Metabolism," etc. This volume will appeal to the lay reader since it has no clinical pictures, diagnostics or therapeutics. It is well worth careful reading.

Abstract Department

Failure to respond to adrenin in different types of failure and death of the heart. (Résistance a l'adrénaline par rapport aux divers processus de la mort du coeur). Bardier, E., Compt. rend. Soc. de biol. **98**: 1408. 1928.

The dying heart fails in different ways, through muscular weakness, sudden spasm of the ventricles, or fibrillation. In dogs, it can be shown that in cases of over dosage of chloroform or of asphyxia the heart responds feebly or fails entirely to respond to injections of adrenin. These are cases where the heart fails slowly through muscular weakness.—J. C. D.

Neural and hormonal factors in bodily activity. The prepotency of medulliadrenal influence in emotional hyperglycemia. Britton, S. W., Am. J. Physiol. **86**: 340. 1928.

Normal cats which have been excited (while caged and displaying only minor muscular activity) by an aggressive dog show marked increments in blood-sugar level. Following two minutes' excitement the glycemic percentage is commonly augmented 30 to 90 per cent; greater increases (up to over 100 per cent) are observed after four minutes' excitation. The hyperglycemic as well as the general reactions become less marked with succeeding emotive responses. Evidences of parallelism in visceral and somatic responses are apparent. Hyperglycemia attending emotional reactions in animals with splanchic branches to the liver severed and normal medulliadrenal function maintained is only slightly modified from the normal. Profound disability of the glycogenolytic mechanism is observed in animals which have been deprived of the adrenal medulla; emotional excitation for two or four minutes in such cases usually results in significant depressions in blood sugar which may persist for twenty minutes or longer. The general affective response is not appreciably altered. The hepatic glycogen in medulliadrenalectomized animals was within the normal limits. The observed emotional hypoglycemia, therefore, was probably referable to failure to mobilize glycogen, in the absence of adrenin secretion, adequately to supply the demands of even minor muscular activity. The importance of medulliadrenal intervention in calling forth readily available fuel for muscular activities during conditions of urgency is pointed out.

—Author's Summary.

Suprarenal-renal heterotopia. Caylor, H. D., J. Urol. **20**: 197. 1928.

Suprarenal-renal heterotopia is the developmental inclusion of cortical and medullary suprarenal tissue beneath the capsule of the kidney. All or only a part of the suprarenal gland may be beneath the renal capsule. The condition is frequently bilateral, it affects males chiefly, and it is usually associated with a thymicolymphatic constitution. The anomaly has surgical importance, for it cannot be recognized before operation. Persons afflicted usually have a status thymicolymphaticus with accompanying susceptibility to surgical shock or infection. There is a potential reduced production of epinephrine, with always the possibility of an acute epinephrine insufficiency following a nephrectomy. Kidneys to be removed should be carefully scrutinized for this anomaly during and immediately after operation, because knowledge of the defect might save the removal of the suprarenal gland during nephrectomy or, if it is inevitable (as it was in the case reported here), the epinephrine insufficiency which might develop would be anticipated.—Author's Abst..

Action of adrenaline on the isolated heart. Chio, M., Arch. di farmacol. sper. **45**: 44. 1928. Abst., Chem. Absts. **22**: 3324.

The frog heart was isolated and left *in situ* with a glass canula penetrating into the venticle through the abdominal cavity, the veins being ligated in such a way as to avoid injury to the chest. Ringer's solution was perfused continuously at a diastolic pressure of about 5 cm. H_2O, and systolic pressure of about 13 cm. H_2O. Under the influence of adrenalin in concentrations of 1:100,000 to 1:10,000,000 the same variations in the work of the heart resulted as were obtained by very light circular compressions on the chest and on the auricles.

A study of the adrenal cortex in the mouse and its relation to the gonads. Deanesly, R., Proc. Roy. Soc. s. B. **103**: 523. 1928.

The two adrenals of the animals were always histologically similar. In the young female about two-thirds of the adrenal cortex may be occupied by a dark staining or X zone. When the female becomes older, this X zone disappears and the cortex becomes similar to that of the male. At three weeks of age the adrenals of both sexes are similar. The inner zone of the cortex disappears in the adrenal gland of the male, but in that of the female it grows rapidly, so that at five weeks it may occupy about half of the cortex. The author from the material at hand cannnot say at what age the X zone begins to break down, but in some cases it may be intact in a 12 weeks' old mouse. This degenerative process is slow. The changes observed in the cortex showed no relationship to the oestrus cycle. Pregnancy causes a rapid and complete degeneration of the X zone. In the males which were castrated, the adrenals increased in size, but there was no increase in size of the medulla. These mice develop an X zone which is similar to the X zone of the adrenal of the female mice. Ovariotomy, however, does not influence the adrenal gland of the female. Adrenalectomy increased the length of the oestrus cycle by one day.—E. L.

Hypotension following adrenin in tabetics (Action hypotensive de l'adrénaline chez les tabétiques). Dumas, A., R. Froment and Miss Mercier, Compt. rend. Soc. de biol. **99**: 76. 1928.

In tabetics, subcutaneous injection of adrenin is followed by a prolonged fall in blood pressure.—J. C. D.

Addison's disease in the negro. Evans, L. S., Am. J. M. Sc. **176**: 499. 1928.

This author believes that Addison's disease is more prevalent among negroes than the literature reveals because of the prevalence of tuberculosis among them. A survey of the Index Medicus listed only one case. Three cases are reported with complete case histories. In one of the cases, the diagnosis was confirmed by autopsy, but the evidence for diagnosis of Addison's disease in the other two cases was good.—E. L.

Carcinoma of the pancreas: clinical observations. Friedenwald, J. and T. S. Cullen, Am. J. M. Sc. **176**: 31. 1928.

This study deals with 37 cases, of which 29 were confirmed by autopsy. Nearly all of the cases were in individuals between 40 and 70 years of age. The initial symptoms were a mild digestive discomfort after meals. As the disease progressed, pain, nausea, vomiting and cachexia were noted. The stools were usually acholic and pasty. The pancreatic secretion usually showed a diminished activity of the ferments. The liver sometimes becomes enlarged,

this being noted in 17 of the cases. The gall bladder may become distended and palpable as a pear-shaped tumor. (Noted in 23 of the cases.) This involvment of the gall-bladder and liver may be recognized by disturbances of the biliary and hepatic functions. Transient glycosuria was observed in 6 cases. Cancer, however, is rarely the cause of diabetes. Diagnosis of cancer of the pancreas can be made in 50 per cent of the cases. The tumor, which is usually located in the head of the pancreas, may be palpated in some instances. The duration of the disease in these 37 cases was only 8 months. Operative treatment has proven unsatisfactory because the malignant growth usually has its seat in the head of the pancreas, which is the most unfavorable for resection.
—E. L.

A case showing underweight unrelieved by fattening with the use of insulin (Cas de maigreur résistant au traitement d'engraissement par l'insuline). Fonseca, F., Compt, rend. Soc. de biol. **98:** 1590. 1928.

The patient showed asthenia, vagotonia, muscular pains, increased sensibility to insulin, and a hypoglycemic curve after a glucose meal. The picture is due possibly to adrenal hypofunction, hence the failure to respond to insulin treatment.—J. C. D.

Observations upon adrenalectomized cats treated with the cortical hormone. Hartman, F. A., F. R. Griffith, Jr. and W. E. Hartman, Am. J. Physiol. **86:** 360. 1928.

A condition simulating chronic adrenal insufficiency was produced by the daily injection of extracts of the adrenal cortex into 108 completely adrenalectomized cats. The symptoms were those of acute insufficiency except that they tend in general to develop more gradually. In a majority of the animals treated with extract, the metabolism remained within normal limits for periods ranging from 7 to 29 days after removal of the second adrenal. The animal never gained weight and usually lost long before the onset of terminal symptoms. These animals were less resistant to cold and infections. They fatigued more readily than did normals. Overeating caused the blood urea to rise, and brought on symptoms of adrenal insufficiency. In a few instances the skin changed from pink to gray in color. A chocolate-brown subcutaneous fat was found in a cat which survived 300 days. Thyroidectomy and gonadectomy (5 cases) apparently did not modify the survival period of treated adrenalectomized cats.—R. G. H.

Functional insufficiency of the suprarenal glands. Mills, C. A., Arch. Int. Med. **42:** 390. 1928.

A functional disturbance common in the tropics and Orient is described and illustrated by a report of 40 cases. The principal features of the disturbance are: (a) hypermotility of the gastro-intestinal tract, with frequent occurrence of cardiospasm, pylorospasm and ileocecal or sigmoid spasm; (b) these motor disturbances may lead to nausea, vomiting, epigastric or abdominal pain and either diarrhea or constipation. The pain and other symptoms may simulate chronic appendicitis, peptic ulcer or tuberculous enteritis; and (c) there is also usually present gastrict hypochlorhydria or achlorhydria, marked vascular hypotension and moderate anemia. Hypoglycemia with high tolerance for dextrose, weakness and loss in weight, urticaria, edema, pigmentation of the skin and menorrhagia also were observed. Foreigners are more susceptible to this trouble than natives. It seems to be definitely related to the coincidental peaks of humidity and heat, when cooling of the body becomes difficult. In some of the foreigners, the onset of trouble was clearly associated with their

first contact with the intense humid heat, while in many others the onset followed their first summer in China. Relief of the symptoms by the oral administration of epinephrine was usually immediate and complete. Autopsy in one case did not show anything to account for the severe condition except changes in the suprarenals characteristic of those seen in animals subjected to moist heat. The conclusion seems justified that suprarenal insufficiency is responsible for the clinical picture presented, and that this represents a distinct disease entity just as truly as does hypothyroidism or hyperthyroidism. Subsidiary conclusions to be drawn from this report are: (a) diagnosis of tuberculous enteritis, peptic ulcer or chronic appendicitis should be made with due caution, to rule out all purely functional disturbances; (b) as a treatment for spastic constipation, the oral administration of epinephrine seems effective and often curative; and (c) many patients with so-called sprue are possibly suffering from suprarenal insufficiency.—Author's Summary.

The lactic acid in muscles of decapsulated rats (L'acide lactique musculaire des rats surrénaloprives). Mazzocco, P., Compt. rend. Soc. de biol. **99**: 174. 1928.

Rats were tested ten, thirty, and sixty days after adrenalectomy. The lactic acid was taken immediately after a minute of tetanization and after intervals of rest following tentanization. The controls showed less lactic acid as well as a more rapid disappearance of it from the muscle than did the adrenalectomized animals.—J. C. D.

Carcinoma of the suprarenal. Neligan, G. E., Proc. Roy. Soc. Med. (Sec. Dis. Child.), **21**: 1321. 1928.

The case described was that of a girl 5 years old. For six months the mother had noticed an increase in size of the child's abdomen. The child complained of occasional abdominal pain. She also appeared to be maturing rather rapidly. On examination, the child appeared several years old than her age. The distension of the abdomen and the left side appeared to be due to a hard, fixed, smooth tumor, which was dull on percussion and did not move with respiration. The pubic hair was well developed. Operation revealed a tumor fixed to the posterior abdominal wall and to the upper pole of the left kidney. The tumor and the left kidney were excised and the child made an uninterrupted recovery. The pathological report was that of solid polygonal and giant celled carcinoma of suprarenal.—I. B.

Addison's disease. Phear, A. G., Proc. Roy. Soc. Med. (Clinical Sec.) **21**: 1167. 1928.

The case described occurred in a woman of 25, who was admitted to the hospital in November, 1927. There occurred marked pigmentation, which was generalized except for the scalp and mucous membrane. It was most pronounced on the face, back of neck, arm and nipples. The blood pressure was low. There were no evidences of alimentary tract or pulmonary disorder. In February, 1928, the patient was again under observation. Pigmentation was more marked, the color being a deep brown; fingers and knuckles were blackish, and the lines of palms of the hands mapped out by deep pigment. The mucous membrane of the cheeks was now involved, and there were a few almost black spots on the arms and legs. The patient had recently suffered from attacks of hiccoughs, which were very severe and lasted from 10 to 15 minutes. There was also marked loss of vigor, though she had worked as a typist. The blood pressure was lower than previously. Treatment did not relieve the symptoms.—I. B.

The influence of blood from the adrenal vein of rabbits before and after a stimulation of the splanchnic nerve on the isolated intestine (Zur Frage des Einflusses von Blut aus der Nebennierenvene des Kaninchens vor und nach einer Reizung der N. splanchnici auf den isolierten). Ptschelina, Alexandra, Ach. f. d. ges. Physiol. **220**: 371. 1928.

Blood contains other substances besides adrenine which have the typical adrenine action on the isolated intestine; following adrenal extirpation, blood taken from other veins has the typical adrenine action of the preparation. Hence the isolated intestine cannot be used as a specific method for showing presence of adrenine in blood.—A. T. C.

Acid-base equilibrium after bilateral nephrectomy. Swingle, W. W., Am. J. Physiol. **86**: 450. 1928.

Bilaterally nephrectomized dogs do not develop intoxication. In some cases a slight fall in alkali reserve may occur, but the change is in striking contrast to the acidosis which follows adrenal removal. Blood sugar increases slightly after total kidney removal, but falls markedly after adrenal extirpation. High figures for inorganic phosphate, sulphate and urea are found after nephrectomy and adrenalectomy. Blood chlorides fall as sulphate and phosphate rise following nephrectomy. The suggestion is made that the acid intoxication of adrenal insufficiency and probably also of uremia is extrarenal in origin, since it is not present in nephrectomized dogs with total suppression of kidney function.—Author's Summary.

Studies on suprarenal insufficiency. 1. The effect of suprarenal insufficiency on reproduction and the oestrus cycle in the albino rat. Wyman, L. C., Am. J. Physiol. **86**: 528. 1928.

Of twenty-eight doubly suprarenalectomized rats which were exposed to males, fifteen became pregnant and thirteen had normal litters. At autopsy eleven of these rats were found to have gross accessory cortical tissue. Of the thirteen that did not become pregnant six died of suprarenal insufficiency and three of the seven that survived had gross accessory cortical tissue. Single suprarenalectomy or a blank operation did not disturb the regular occurrence of oestrus cycles. Forty-one female rats of breeding age were studied by the vaginal smear method both before and after double suprarenalectomy. In sixteen of twenty-three rats which died of acute or subacute suprarenal insufficiency there was practically complete inhibition of oestrus after operation. In six of eight rats which died of chronic suprarenal insufficiency there was marked prolongation of the dioestrus pauses after operation. In eight of ten rats which survived until they were killed for autopsy from three to four and a half months after operation there was no serious disturbance in the occurrence of oestrus cycles. Seven of this group of ten were found to have gross accessory cortical tissue. The use of a vital dye selective for the corpora lutea in four cases showed that persistent dioestrus after suprarenalectomy as shown by the vaginal smear is due to suspension of ovulation. Weight changes after suprarenalectomy were correlated with the clinical findings and the oestrus history, indicating a disturbance of metabolism. The body temperature changes that occurred after suprarenalectomy were not sufficient to account for the disturbance in the oestrus cycles. It is concluded that suprarenal insufficiency in rats results in partial or complete inhibition of oestrus, the degree of disturbance of ovarian function being correlated with the severity of the insufficiency. It is suggested that the relationship between the functioning of the suprarenal glands and the gonads is not direct, but that it is indirect through the mediation of other factors, probably metabolic in nature.—R. G. H.

The influence of adrenalin on the human spleen and blood picture. Yang, C. S., Chinese J. Physiol. **2**: 163. 1928.

Subcutaneous injection of adrenalin was found to markedly decrease the size of the spleen in patients with splenic enlargement. Simultaneously the hemoglobin, red blood cells and white blood cells definitely increased the splenic contraction. A smaller increase was found to occur in the blood cellular elements of normal persons. On the contrary, in splenectomized patients no increase of the red cells or hemoglobin was caused by adrenalin injection, but there was an increase of white cells, though not as marked as with normal or splenomegalic persons. The author assumes that this increase of cellular elements is produced by the mechanical squeezing of the contracted spleen following the adrenalin injection, thus confirming the work of Barcroft that the spleen acts as a reservoir of blood.—L. G. Kilborn.

Headache. Drury, D. W., New England J. Med. **199**: 167. 1928.

The author includes, in his general consideration of the causes of headache, a series of cases of endocrine disorders in which headache was the presenting symptom. These involved disturbances of the pituitary, thyroid, or gonads.
—J. C. D.

The vegetative nervous system, hypercholesteremia and arteriosclerosis (Vegetative Nervensystem, Hypercholesterinamie und Arteriosklerose in Ihren Beziehungen zu Einander). Glaser, F., Klin. Wchnschr. **6**: 2377. 1927.

The author quotes numerous references in the literature to show a relationship between the autonomic nervous system and the blood lipoids (cholesterol and lecithin). He further reports eight cases in which he observed a rise in the blood cholesterol following sympathetic stimulation by the subcutaneous injection of 1 mg. adrenalin. He believes there is a relationship between the activity of the vegetative nervous system and hypercholesterolemia and the development of arteriosclerosis.—S. Shapiro.

A hormone mechanism for gall-bladder contraction and evacuation. Ivy, A. C. and E. Oldberg, Am. J. Physiol. **86**: 599. 1928.

The injection of the following substances into the duodenum of the dog caused the gall-bladder to contract with the animal under light barbital-ether anesthesia: 15 to 40 cc. of N/10 HC1, 30 cc. of butter, digested egg yolk, cream and olive oil, 0.5 per cent butyric acid and 5 per cent soap solution. Undigested olive oil, egg-yolk and cream were ineffectual. Spontaneous rhythmic contractions of the gall-bladder were observed to occur from 2 to 4 times a minute. A small dose of "cholecystakinin" would usually increase their amplitude to as much as 3 cm. of bile pressure; a large dose would usually cause them to disappear at the height of the contraction, but they would reappear some time during the period of relaxation. If they were not present prior to the injection, they would frequently appear during the latter part of the period of relaxation. We have observed the hepatic ducts to be injected with lipoidol during the contraction of the gall-bladder, the injection of the ducts being due, we believe, to increased (abnormal?) tone of the duodenum or sphincter of Oddi.—Authors' Abst.

Results of castration in turkeys (Influence de la castration chez le Dindon). Athias, M., Compt. rend. Soc. de biol. **98**: 1606. 1928.

The usual loss of male characters in structure, voice, and instinct follow castration.—J. C. D.

The development and morphology of the gonads of the mouse. Part III. The growth of the follicles. Brambell, F. W. R., Proc. Roy. Soc. S. B. **103**: 258. 1928.

In this microscopic study of the ovary of the mouse, the author has found the following: In any one ovary, oocytes at all stages between the smallest (13 μ) to the full grown (70 μ in diameter) may be found. At the time the oocyte is mature, the follicle is 125 μ in diameter. The growth of the follicle and oocyte are correlated up to this point, but afterwards the follicle increases in size independently of the oocyte. The subsequent changes in the oocyte do not increase the size, but the follicle may grow to 550 μ in diameter. Ovulation in the mouse takes place during late pro-oestrus or very early oestrus. The average number of follicles maturing at the oestral period was 9.3.—E. L.

The regulation of the contracting uterus by hormones (Recherches expérimentales sur la régulation hormonale de la contractilité utérine). Brouha, L. and H Simonnet, Arch. Internal. de physiol. **29**: 94. 1927.

From the experimental results there are two distinct actions of the follicular liquid. The specific female sex hormone which regulates the development of the uterus is called *folliculine*. The one which caused rhythmic contraction of the uterus in vitro is called the oxytocic hormone. The effect of oxytocic hormone is similar to that of pituitrin.—E. L.

Physiology of the corpus luteum. I. The effect of very early ablation of the corpus luteum upon embryos and uterus. Corner, G. W., Am. J. Physiol. **86**: 74. 1928.

This paper reports experiments designed to test again Fränkel's results on the indispensability of corpora lutea for the maintenance of pregnancy in the rabbit, and Bouin and Ancel's results on the necessity of these glands for the pre-gestational proliferation of the endometrium. Three sets of experiments resulted as follows. (1) After ablation of both ovaries no ova survive the early blastocyst stage and the endomentrium fails to proliferate as in early pregnancy. (2) After removal of one ovary and half-resection of the other, or after resection of both ovaries, with as little as one-fourth of the ovarian tissue remaining, so long as this contains one or more corpora lutea, the embryos develop normally in a normal proliferating uterus. (3) After removal of all of the corpora lutea with survival of one-sixth to one-half of the ovarian substance, the results are similar to those following double oöphorectomy, though with some unexplained irregularities. The experiments make it seem likely that in the so-called "premenstrual" stage the human endometrium develops likewise under the influence of the corpus luteum.—Carl Hartman.

Note on the ovarian hormone: Influence of the corpus luteum on the oestrous cycle (A propos des hormones ovariennes: Influence du corps jaune sur le cycle oestrien). Cotte, G. and G. Pallot, Compt. rend. Soc. de biol. **99**: 69. 1928.

Human corpora lutea were grafted into two groups of female rats, one group of which was spayed and the other normal. If the corpora had been removed during the latter half of the menstrual cycle, they had an inhibitory action on the cycle in the rats. If removed from the human earlier than the 14th day after menstruation began, they had a double action. In the spayed rats there were one or two oestrus cycles and in the normals prolonged and accelerated cycles. This stimulating effect was then followed by an inhibitory one, as with the older corpora.—J. C. D.

The relation of insulin to ovulation (L'insuline et ses rapports avec l'ovulation). Cotte, G. and G. Pallot, Compt. rend. Soc. de biol. **99**: 74. 1928.

Injection of therapeutic doses of insulin into rats is followed by cessation of the oestrus during the treatment. The ovaries show no ripe follicles, atresia of numerous follicles, and apparently destuction of the ovum in the primordial follicle.—J. C. D.

Irradiation of ovaries and hypophysis in disturbances of menstruation. Drips, Della G. and Frances A. Ford, J. A. M. A. **91**: 1358. 1928. Abst. A. M. A.

The continued study of a group of cases of primary oligomenorrhea and amenorrhea and of menorrhagia and metrorrhagia has further convinced the authors of the existence of an essential ovarian hypoactivity in both conditions. The occurrence of spontaneous remissions and the variable results with all forms of treatment add difficulty to the evaluation of a new method. Low dosage irradiation of the ovaries or hypophysis offers an additional therapeutic measure in intractable cases. The low dosage irradiation has given a comparatively high percentage of favorable results in view of the severity of symptoms in the cases in which it has been used, and regulation, when attained, has continued over a relatively long period. In experimental studies, which are still incomplete, an attempt was made to gauge the amounts of Roentgen rays for application to the ovaries of white rats which might be comparable to low dosage irradiation in the human being. Certain immediate variations in the estrual cycle without disturbance of late regularity were obtained. In most instances fertility was not affected. The second and third generations of the irradiated rats were normal. It was not possible to demonstrate precocious sexual development of immature rats by irradiation of the hypophysis with varying amount of Roentgen rays.

On the relation between the number of corpora lutea in the rabbit and the degree of preparation in the uterus for implantation (Sur les relations entre le nombre de corps jaunes et le degré de préparation de l'utérus a la nidation de l'oeuf chez la Lapine). Joublot, J., Compt. rend. Soc. de biol. **98**: 1541. 1928.

The changes in the uterus in preparation for implantation depend on the presence of corpora lutea. If the lutean material is reduced below a minimum (between one and two corpora), the changes in the uterus are not as intense as normal, though reaching their maximum at the normal time. More lutean material than the minimum does not intensify the reaction in the uterus beyond the normal.—J. C. D.

Female (Sexual) Hormone: Menformon and standardized ovarian preparations. Laqueur, E. and S. E. De Jongh, J. A. M. A. **91**: 1169. 1928.

In answer to the demand for exactly standardized ovarian hormone, Ernst Laqueur and S. E. De Jongh, Amsterdam (Journal A. M. A., Oct. 20, 1928), recommended the standardized, limpid, watery solution of the Menformon, whose preparation and development is essentially based on the American discoveries. Menformon has been in clinical use for two years and a half and for two years it has been available commercially in Europe. The degree of purity obtained in preparations of Menformon is already considerable (0.0008 mg. per mouse unit in the best preparations). Other points of importance are its solubility in water and its power to dialyze through membranes and to resist various agents. On the biologic side, the most remarkable facts are that Menformon is able to produce true estrus in castrated immature or senile rodents; to induce

growth of the juvenile uterus in all species of mammals observed up to this moment, and to cause development of the secretory as well as that of the external parts of the mammae not only in females, but also in males, whether these are castrated or normal. Further, Menformon specifically increases metabolism only in female, and not in male castrates; it has an antimasculine effect in decreasing the velocity of development of the sexual organs in young male animals and in reducing the size of these organs in adult males. Its occurrence in the blood and urine opens up the possibility of computing a hormone balance for various individuals. Another interesting feature is its presence in small amounts in the testes and in urine of normal men. In view of its perfect harmlessness even when large doses are injected intravenously (up to 2,000 mouse units in dogs), we felt justified in advising the use of Menformon in clinical practice; it may be administered subcutaneously as often as required, as clinical experience has shown that this method of administration is devoid of danger.

The influence of follicular liquid from a case of nymphomania on the vaginal smear in the rat (Influence du liquid folliculaire provenant d'une nymphomane sur la réaction vaginale du rat). Cotte, G. and G. Pallot, Compt. rend. Soc. de biol. **98**: 1336. 1928.

The liquid, when injected into a spayed rat, produced typical oestrous changes in the vaginal smear. Blood taken from this same case during the premenstrual period also gave similar changes when injected.—J. C. D.

Reactivation of the senile ovary and the whole female organism by hormonal procedure (Reaktivierung des senilen Ovars und des weiblichen Gesamtorganismus auf hormonalem Wege). Steinach, E., H. Kun and W. Hohlweg, Arch. f. d. ges. Physiol. **219**: 325. 1928.

Experiments were made with senile female rats 2 to 5 months after cessation of oestrual cycles, when typical appearances of senility were present, including loss of hair, partial baldness, bowed attitude, somnolence, and anemia. Following the administration of the active hormonal preparation, there was a recommencement of normal estrus, regeneration of the ovaries (microscopically detectable by the re-occurrence of large ripe follicles and fresh corpora lutea, and functionally shown by the occurrence of spontaneous cycles after cessation of injection), regeneration of the uterus, growth of hair and disappearance of baldness, improved circulation, strengthening of body musculature and increase of nerve irritability (illustrated by the regaining of the former elasticity of force of movement), and finally increase of metabolism, with increased appetite and gain of weight. The psychical re-awakening corresponded.—A. T. C.

Effect of high temperature on the gonads of frog larvae. Witschi, E., Proc. Soc. Exper. Biol. & Med. **25**: 720. 1928.

Frog larvae which had been raised under nearly optimal conditions up to the 7th week were subjected after the 34th day to the maximal temperature that can be endured permanently, 32° C. The gonads of both males and females grew much slower than those of normal controls. However, the spermatogonia of the testis were of about normal size and the seminiferous tubules differentiated in a typical way. The reactions of the ovaries are more complex and more important. At the time when the temperature was raised the ovaries contained large numbers of young ovocytes in the synapsis stage. Two weeks later this type of germ cells had completely disappeared. The ovogonia

are still present and the deeper layers of the cortex contained large auxocytes. The latter, however, were in degeneration. Their nucleoli were extremely large and basophilic and the ovoplasm contained coarse granules. Immediately after the differentiation of further ovocytes had come to an end, the medullary part of the ovarial sac (rete ovarii) transformed into a typical rete testis, vasa efferentia and seminiferous tubules. At first the latter completely lacked germ cells. However, sooner or later the ovogonia migrated from the cortex to the medulla, and after having entered the seminiferous tubules transformed into spermatogonia. Thus the experiment led to the total reversal of sex of the females. The normal controls consisted of 100 females and 96 males. The experimental group contained no typical females after the second week of rise in temperature; but between the 15th and 33rd day 53 females in different stages of sex transformation and 62 typical males were preserved.

—Author's Abst.

A hormone of heart movement. X. Warm blood experiments with the heart hormone preparation (Ueber ein Hormon der Herzbewegung. X. Warmblüterversuche mit dem Herzhormonpräparat). Haberlandt, L., Arch f. d. ges. Physiol. **220**: 203. 1928.

Results similar to those given by frog hearts were obtained with rabbit hearts.—A. T. C.

A case of diabetes insipidus caused by hypernephroma metastasis in the midbrain. Elmer, A. M., J. Kedzierski and M. Scheps, Wien. klin. Wchnschr. **41**: 591. 1928.

A case of diabetes insipidus which came to autopsy and revealed a hypernephroma metastasis in the midbrain, with little or no involvement of the pituitary gland, is reported. The urinary output was about 5 liters daily, and the urine contained 0.1 per cent of sugar. The blood sugar was 230 mgm. On a low carbohydrate diet, the blood sugar fell to 110 mgm. Protein injections and various pituitrin preparations were without effect on the polyuria, and insulin given with pituitrin increased the urine volume. The polyuria and glycosuria are explained as the result of the destruction of water, salt, and sugar metabolism regulating centers in the midbrain.—R. B. Gibson.

Case of dyspituitarism. Worster-Drought, C. and B. W. C. Archer, Proc. Roy. Soc. Med. (Neurol. Sec.) **21**: 1513. 1928.

The patient was a male of 15 who was of unusual size for his age and presented excessive obesity, difficulty in walking, attacks of vomiting and mental backwardness as the outstanding clinical features. He did not walk until nearly three years old, and between three and four he began to grow in stature rapidly and became much more obese than the average child of his age. At that time it was noticed that he was backward mentally. He was entered at school at the age of 5, but made no progress and has never learned to read or write, though he has shown some interest in mechanical things. Attacks of vomiting at night were frequent, but there were no headaches. Sight and hearing were good. There appeared to be no significant points in the family history except that the father's appearance suggested acromegaly. Examination of the patient revealed the height of 73 inches, with typical physical evidences suggestive of dystrophia adiposo-genitalis.—I. B.

Effect of ligature of pancreatic ducts on the regulation of the glycogen titer. Caccuri, S., Boll. d. Soc. ital. di biol. Sper. **2**: 918. 1927. Abst., Chem. Absts. **22**: 3440.

The pancreatic ducts of 4 dogs were ligated and every 15 days dextrose solution was injected by way of the jugular vein and the free and combined sugar was determined. Two dogs died, but in the remaining after 75 to 90 days it was found that after injection of sugar the combined sugar increased, while free sugar diminished; i. e., similar results as would result from insulin injection. Apparently a tolerance for sugar is gradually acquired. The pancreas was found atrophied and changed almost wholly to connective tissue.

Action of insulin on the capillary circulation. Cuenca, B. S., Rev. med. de Barcelona, **9**: 398. 1928. Abst., Physiol. Absts. **13**: 295.

Experiments are detailed to show that insulin has a vaso-dilator action on small capillaries. The effect of insulin on producing a more rapid passage of glucose into muscle is thus due to its vaso-dilator action on the muscle capillaries.

Changes in the blood sugar of normal subjects following treatment of the pancreas with x-ray (Modifications de la glycémie chez des sujects normaux par l'irradiation du pancréas).

Effect of irradiating the pancreas on the glycemia and glycosurea in diabetics (Action de l'irradiation du pancréas sur la glycémia et la glycosurie des diabétiques). Fonseca, F. and C. Trinaco, Compt. rend, Soc. de biol. **98**: 1591-1592; 1593-1594. 1928.

In the normals, one-half of an erythematous dose produced a reduction in blood sugar and a change in the curve following glucose ingestion, probably due to an increased output of insulin. In three diabetics, the glycosurea and hyperglycemia were reduced for several days.—J. C. D.

Ocular complications of diabetes. Gifford, S. R., M. Clin. North America, **12**: 423. 1928.

True cataract may occur, but is rare, while senile cataract occurring in the diabetic is common and does not differ from cataract in the non-diabetic. With a little pre-operative care to reduce the urinary sugar to the minimum, operation in these cases is not attended by any great risk. Cataract and rapid changes in refraction occurring in diabetes are probably the result of changes in the osmotic pressure of the blood. Retinitis occurs chiefly in diabetics past the age of 50, often with renal or vasular complications, but also without any signs of these. It may be the only sign of an abnormal condition of the vessels in these patients. The prognosis for life and vision is relatively good in diabetic retinitis, in contrast to that of albuminuric retinitis.—I. B.

Simultaneous stimulation of the external and internal secretions of the pancreas (Excitation simultanée de la sécrétion externe et de la sécrétion interne du pancréas). Gley, E. and R. Hazard, Compt. rend, Soc. de biol. **99**: 16. 1928.

The injection of hydrochloric acid into the duodenum stimulates the external secretion of the pancreas. It, likewise, increases the production of insulin, as is shown here by studies on the blood sugar changes in dogs.—J. C. D.

The effect of insulin upon polyuria in diabetes insipidus; the combined effect of insulin and pituitrin upon water metabolism. Klein, O. and H. Holzer, Deutsche Arch. f. klin. Med. **156**: 111. 1928. Abst., Chem. Absts. **22**: 3458.

The attempt has been made to employ for differential diagnosis the effect of insulin upon the diuresis of diabetes insipidus; but there is not sufficient justification, since the hypo- and hyperchloremic forms are not so easily distinguished by their reaction to insulin alone. In those cases where insulin alone was observed to be without diuretic effect, the effect became manifest when pituitrin was injected with the insulin. The antidiuretic effect of insulin is then an intensification of the effect of the pituitrin. In a case of syphilis, where the hypophysis was seriously affected, the antidiuretic effect was entirely lacking when insulin alone was administered; in similar cases which did not involve the hypophysis the effect was definite. In a case of lesion of the hypophysis the diuretic effect was observed only when insulin and pituitrin were injected together. The results were influenced quantitatively by the size of the dose, and by the amounts of water and of carbohydrate consumed during the experiment. The use of insulin produces perfectly regular results where carbohydrate metabolism and the water-binding ability of the organism are seriously disturbed. The effect of the insulin is upon the carbohydrate metabolism, and only indirectly upon the diuresis.

Synthalin in diabetes mellitus. Lyon, D. M., Edinburgh M. J. **35**: 357. 1928.

Fourteen diabetics were used and tested either for the ability of synthalin to clear up glycosuria without insulin or its power to maintain a satisfactory carbohydrate balance after insulin had been used. Synthalin had a distinctly favorable action under both of these conditions.—J. C. D.

Prolonged insulin hypoglycemia without symptoms. Maddock, S. J. and H. C. Trimble, J. A. M. A. **91**: 616. 1928. Abst., A. M. A.

In connection with some experiments on the corpuscle-plasma distribution as related to insulin shock, the authors were particularly impressed by the length of time that hypoglycemia can exist before symptoms appear. Experimental evidence shows that, following insulin administration, the blood sugar of diabetic patients and depancreatized dogs may remain at levels of 50 mgm. per cent or below for from one to six hours without symptoms. Such periods may or may not be followed by hyperglycemic reactions. They believe that this phenomenon, whose dangers are evident, is probably frequent in occurrence; that it usually is unrecognized, and that it may account for the difficulty so often encountered in regulating the administration of insulin. It is tempting to the authors to reason by analogy that if continued high blood sugar overstrains the pancreas, continued low blood sugar may over rest it.

Experiments on fats and lipoids in blood. IV. The partition of fats and lipoids in the blood of dogs with pancreatogenic diabetes after insulin injection (Untersuchungen über Fette und Lipoids im Blute. IV. Ueber die Verteilung der Fette und Lipoide im Blute nach der Insulininjektion bei Hunden mit pankreatogenem Diabetes). Morimoto, M., Arch. f. d. ges. Physiol. **219**: 733. 1928.

The fat and lipoid content of blood decreases following total extirpation of the pancreas. A marked increase takes place in such animals following injection of insulin. The corpuscular content is not changed, nor is the ratio of cholesterol to total lipoid, by either pancreatectomy or insulin injection; the changes take place in the plasma.—A. T. C.

Diabetes mellitus and pregnancy. Walker, A., Proc. Roy. Soc. Med. (Sec. Obs. & Gynec.) **21**: 377. 1928.

This paper gives the results of a thorough search of the available records for cases of diabetes mellitus and pregnancy, with a view to showing that since the use of insulin one may be justified in disregarding the advice given in most textbooks that it is extremely dangerous for a diabetic woman to become pregnant, and that, if unfortunately she does, pregnancy should be terminated. From the data collected it appears that the administration of insulin has entirely altered the outlook for the better in cases of pregnancy complicated with diabetes, as it has done in diabetes generally. Although diabetes is itself a very serious disease, and must be regarded as a serious complication of pregnancy, if the patient is treated with insulin and placed on a proper diet there seems to be no ground for terminating the pregnancy, and there is no reason why she should not give birth to a live child. There appears to be no special incidence of puerperium complications. Pregnancy does not appear to have any ill effects on the diabetic condition. Apparently in one case insulin has been the means of curing sterility.—I. B.

The value of acterol (irradiated ergosterol) in the treatment of thyroparathyroidectomized dogs. Brougher, J. C., Am. J. Physiol. **86**: 538. 1928.

"Acterol" in 0.4 cc. dosage, when given along with milk to twelve dogs from the day of operation, prevented the development of violent tetany. Animals which did not retain their milk and thus had no source of calcium showed tetany in spite of the acterol. Recovery was quicker in parathyroidectomized dogs given acterol than cod liver oil. The time for recovery ranges from 15 to 30 days for acterol and 30 to 40 days for cod liver oil. It would seem that a rich supply of vitamin D is efficacious in a large percentage of instances in enabling the body to utilize calcium in the disturbed calcium metabolism found in parathyroid tetany.—R. G. H.

The effect of thyroxin on the respiratory and nitrogen metabolism of a normal subject following prolonged nitrogen-free diet. Deuel, H. J., Jr., Irene Sandiford, Kathleen Sandiford and M. Boothby, J. Biol. Chem. **76**: 407. 1928.

The administration of thyroxin to a normal subject after the depletion of the supply of deposit protein by a nitrogen-free diet for a preliminary period of 30 days did not in any way alter the characteristic effect of the thyroxin on the nitrogenous or respiratory metabolism. However, in spite of an increased urinary nitrogen, which reached a mixmum 7 days after the injection of 7 mgm. of thyroxin, there was no change in the creatinine or uric acid elimination, indicating that the endogenous nitrogen metabolism was not augmented. In a later period the maintenance of the respiratory metabolism at an elevated level by the daily administration of small doses of thyroxin only slightly increased the total urinary nitrogen without changing the creatinine or uric acid output.—H. J. Deuel, Jr.

Endemic goiter in Massachusetts. Doering, C. R., H. L. Lombard and Fredrika Moore, New England J. Med. **199**: 143. 1928.

The report is based on the study of 12,270 high school students. The authors conclude that: The partial correlation between the incidence of goiter and the iodine in drinking water shows that the important variable is distance from the ocean. The presence or absence of communicable diseases, enlarged tonsils, adenoids, cervical glands, dental caries, has no apparent effect on goiter

incidence. The mean weight of children with goiter is slightly less than that of non-goitrous children, though this may be apparent rather than real.

—J. C. D.

A case of post-operative tetany. Hunter, D., Proc. Roy. Soc. Med. (Clin. Sect.) **21:** 1409. 1928.

The case described was that of a woman 44 years old, in whom a sub-total thyroidectomy was performed for the relief of a large endemic goiter. Two weeks after operation symptoms of tetany developed. Four years after operation these disappeared and there were no symptoms for six years, following which they recurred and became more severe than before. Under Collip's parathyroid serum and occasional thyroid opotherapy, relief was complete, but unless treatment was continued the symptoms recurred.—I. B.

The thyroid and atropine. Ikonen, M. W. and S. M. Kusnetzowa, Ztschr. f. d. ges. exper. Med. **57:** 353. 1928. Abst., Chem. Absts. **22:** 3201.

Four parts of serum, one part of an atropine solution and one drop of benzene were mixed and placed in an incubator at 37° for 24 hours. Two drops of the mixture were then placed in one eye of a cat and the pupillary dilation and paralysis observed. The serum of normal rats will neutralize up to a 1:50 solution of atropine. Following thyroidectomy, this power is lost, but returns when thyroid gland is transplanted. Similar results are obtained in patients with thyroid disorder and the method is suggested as a test for thyroid secretion.

Diabetes and hyperthyroidism. Joslin, E. P. and F. H. Lahey, Am. J. M. Sc. **176:** 1. 1928.

The symptoms found in both these diseases are somewhat similar. In 228 cases of primary hyperthyroidism there were 38.6 per cent with glycosuria. The standard for a diagnosis of diabetes in hyperthyroidism is that the blood sugar should be 0.15 per cent fasting or 0.20 per cent or more after meals, in addition to glycosuria. The authors believe that the hyperthyroid patient is more prone to diabetes than an ordinary individual.—E. L.

The crisis of exophthalmic goitre.—Lahey, F. H., New England J. Med. **199:** 255. 1928.

This is a general discussion with an outline of the author's methods of treatment. He concludes that: Thyroid crises are by no means rare. The mortality rate in patients permitted to advance into a state of crisis is extremely high. Treatment in this condition is most effectual if vigorously applied when the first signs of the condition appear. The possibility of the onset of a thyroid crisis during treatment must be considered when conservative treatment is adopted in a patient with thyroidism.—J. C. D.

The familial incidence of exophthalmic goiter. Morrison, H., New England J. Med. **199:** 85. 1928.

This report covers three instances of family goiter, in one of which six cases occurred.—J. C. D.

The effect of iodine and thyroid feeding on the thyroid gland; an experimental study. Mosser, W. B., Surg. Gynec. Obst. **47:** 168. 1928.

Three groups of dogs were studied. In the first group after a section had been removed for microscopic examination the dogs were given Lugol's solution, 10 minims daily for 6 weeks, and then a second biopsy was done. After

an interval of several months during which no medication was given a third biopsy was done. In the second group, after preliminary biopsy the animals were given thyroid extract in increasing quantities until they exhibited symptoms of hyperthyroidism. A second section was taken. Iodine (Lugol's) was then given for 6 weeks, and then a third biopsy was done. After a rest period of 3 months a fourth section was taken. In the third group the treatment was the same as in the second, with the exception that thyroid extract was continued during the 6 weeks that Lugol's was being given. The results, compared with a series of clinical cases, led to the following conclusions: In the experimental animal iodine stimulates the cells to produce colloid. Colloid retention compresses and flattens the cells of the acini. The same effect occurs from iodine administration in the presence of experimental hyperthyroidism. Prolonged iodine administration to a hyperthyroid animal produces a stage of exhaustion in the gland. The effect of iodine on the normal human gland is similar to that in the dog. The effect of iodine on the hyperplastic toxic goiter is similar to that obtained in the normal gland of the dog. After prolonged administration of iodine (3 to 12 months) to the patient with hyperplastic toxic goiter a stage of exhaustion is noted which is similar to that produced in the dog by prolonged feeding with thyroid extract and iodine. The clinical status of the patient is not proportionate to the histological picture when iodine has been taken for a prolonged period. Plummer's theory of the action of iodine is rejected, and another theory based on exhaustion of the gland by continued iodine stimulation is put forward.—A. T. C.

Tetany following thyroidectomy. Pratt, G. P., M. Clin. North America, **12**: 319. 1928.

The case described was that of a woman of 31 years, presenting the symptoms of tetany following thyroidectomy for exophthalmic goiter. The symptoms occurred six weeks after operation, and were heralded by cramplike pains in the hands and feet, with severe nose bleed. The author states that 14 per cent of patients operated upon for goiter present symptoms of latent tetany, unrecognized until an infection, a menstrual period, a surgical operation, or some other disturbance sets in. The principle of treatment is the administration of calcium salts and Collip's serum.—I. B.

Experiments on the action of some iodine compounds of frog larvae (Untersuchungen über die Wirkung einiger Jodsubstanzen auf Froschlarven). Schwaibold, J., Arch. f. d. ges. Physiol. **220**: 1: 1928.

Iodine produces in frog tadpoles no definite "thyroxine" metamorphosis, but a positive effect on the development, shown especially by a shortening of the time of actual metamorphosis. The action is specific to iodide, and is not given by chloride or bromide. Milk from cows fed iodide produces only this effect. An iodoprotein, "Iodtropon," also produces the effect of inorganic iodide only, evidently through the breaking off of iodine during gastric digestion. The same result is also obtained when tyrosine and sodium iodide are fed together to tadpoles.—A. T. C.

On the influence of South-Bavarian goiters on tadpoles and remarks on the technique (Studien über Südbayerische Kröpfe im Kaulquappenversuch und Bemerkungen zu dessen Methodik). Spatz, H., Ztschr. f. Biol. **87**: 41. 1927.

The metamorphosis promoting action of human goiter substances on tadpoles was studied. A uniform tadpole material was used. The thyroid glands were obtained at biopsy, dried and pulverized. One dose of the powder was

fed to the tadpoles, which were otherwise, like the controls, fed on calf's liver. The control group was fed a standardized thyroid preparation. On an average the goiter substances showed the same activity in the human body and on the tadpoles. Hypothyroid goiters and goiters of adolescents had no activity. Clinically indifferent goiters accelerated metamorphosis less than the standard thyroid preparation. Hyperthyroid goiters had a strong effect (one exception). Goiters consist of histologically widely different parts; the different parts also vary in their biological action on tadpoles. The biological activity of a goiter is not bound to one histological structure, but is connected sometimes with tissue rich in colloid, sometimes with cellular tissue. On the whole, tissue rich in colloid is more active.—G. T. Cori.

Hyperthyroidism without visible or palpable goiter. Tucker, J., Am. J. M. Sc. **176**: 504. 1928.

Three cases of hyperthyroidism in which there was no visible or palpable goiter are presented. The soft tissues mask the goiter and the indication for operation is hyperthyroidism and not goiter.—E. L.

The influence of the thyroid on the higher nerve function of dogs. I. The action of single doses of thyroid on conditioned reflexes under simple experimental conditions (Ueber den Einfluss der Schilddrüse auf die höheren Nerven funktionen der Hunde. I. Die Wirkung von Thyreoidea-Einzelgaben auf die bedingten Reflexe bei einfachen Versuchsverhältnissen). Zawadovsky, B. M. and A. L. Sack, Arch. f. d. ges. Physiol. **220**: 155. 1928.

For the first few days there is a phase of general suppression of conditioned reflexes, shown especially as a disturbance of, or incomplete suppression of work-differentiation. In the second stage there is a general increase of irritability, shortening of the latency period, and an increase of both the conditioned and unconditioned salivary secretion.—A. T. C.